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## SIMMONDS' DISEASE AND ANOREXIA NERVOSA

HENRY B RICHARDSON, M D

NEW YORK

In 1914 Simmonds<sup>1</sup> described the destruction of the anterior lobe of the hypophysis which he observed at autopsy in certain cases and reconstructed from the history the clinical picture of the disease which now bears his name. Later<sup>2</sup> (1916 and 1918) he published reports of 4 more cases. In 1933 Silver<sup>3</sup> collected reports of 41 cases and added 1 of his own, in all of which the diagnosis was proved at autopsy, destruction by one lesion or another being present in the anterior lobe. Many other cases have been reported in which the diagnosis was made clinically, recent examples being those of Howard and Rhea<sup>4</sup> (1936) and Regester and Cuttle<sup>5</sup> (1937). Smith<sup>6</sup> (1930) removed the anterior lobe of the hypophysis of the rat without injury to the hypothalamus and provided an experimental counterpart of the disease. He showed also that the deficiency could be remedied by the implantation of pituitary glands. Most of the conditions therefore seemed to be fulfilled for the accurate diagnosis and treatment of the disease in man.

In spite of all this the diagnosis during life remains completely uncertain. The reason is that most if not all the symptoms which are listed as characteristic of Simmonds' disease can be produced by simple inanition. This statement is based on studies reported in the literature and on the study of patients to be reported on here. The emaciation, appearance of age, gonadal atrophy, dental caries, splachnomicria and depression of the basal metabolism may all be interpreted as the result of starvation. In 1874 Sir William Gull<sup>7</sup> observed in young persons

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From the New York Hospital, the Department of Medicine, Cornell University Medical College, and the Russell Sage Institute of Pathology.

1 Simmonds, M. *Deutsche med Wchnschr* **1** 322, 1914, *Virchows Arch f path Anat* **217** 226, 1914.

2 Simmonds, M. *Deutsche med Wchnschr* **42** 190, 1916, **44** 852, 1918.

3 Silver, S. Simmonds' Disease (Cachexia Hypophyseopriva). Report of a Case with Postmortem Observations and a Review of the Literature, *Arch Int Med* **51** 175 (Feb) 1933.

4 Howard, C P, and Rhea, L F. *Internat Clin* **1** 1, 1936.

5 Regester, R P, and Cuttle, T D. *Endocrinology* **21** 558, 1937.

6 Smith, P E. *Am J Anat* **45** 205, 1930.

7 Gull, W W. *Tr Clin Soc London* **7** 22, 1874.

symptoms which were the same as most of those now listed under the heading Simmonds' disease—the emaciation, the scaphoid abdomen, the amenorrhea and the appearance of age. The depression of the basal metabolism is clearly evident in his observation of the slow pulse and subnormal temperature, and he even recommended the use of external heat in the treatment. He made shrewd observations as to the psychic behavior of the patients. In particular he noted their sense of well-being and their excessive activity, in spite of extreme emaciation. He pointed out that this degree of activity would be impossible if the inanition were due to constitutional disease. After discussing hysteria he chose the term *anorexia nervosa* as a name for the disease. As he pointed out, all the symptoms could be explained as the result of inanition, which in turn was due to a "morbid mental state." Nearly all the patients got well with a combination of medication, nursing care and special diet, this was at a time when the function of the pituitary body was unknown and replacement therapy was quite beyond the reach of the imagination.

In 1873 Lasègue<sup>8</sup> published a detailed description of the development of the disease and displayed an understanding of the problem that was at least a generation ahead of that of his contemporaries.

Since the time of Gull many articles have appeared on *anorexia nervosa*, a recent contribution being the exhaustive paper by Ryle<sup>9</sup> (1936), who has observed 51 patients with this disorder. These articles constitute a stream of thought which until recently has run a separate course from the work on Simmonds' disease without any clear statement of the need of applying both concepts to the differential diagnosis in an individual case. It is only recently that the relation has been discussed at all and then only from the point of view of one disease or the other. In spite of all the knowledge which has accumulated since the time of Gull and in spite of the development of psychiatry, the problem presented by the patient is much the same as it was in 1874.

#### METHODS

The tests were performed in the department of laboratories of the New York Hospital and in the Russell Sage Institute of Pathology. The metabolism was studied with the Benedict-Roth apparatus, the standards of Aub and Du Bois being used. The sugar content of the blood was determined by the latest method of Benedict, which does not include the nonfermentable substances and therefore gives readings below those reported by Folin and Wu. The vaginal smears were prepared in the laboratory of Dr. George N. Papanicolaou<sup>10</sup> (1936) of the department of anatomy of the Cornell University Medical College and interpreted by him. The preparation used in the treatment was an extract of the anterior lobe of the hypophysis containing 10 rat units per cubic centimeter and similar amounts of

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8 Lasègue, C. *M. Times & Gaz* **2** 265, 1873.

9 Ryle, J. A. *Lancet* **2** 893, 1936.

10 Papanicolaou, G. N., and Shorr, E. *Am. J. Obst. & Gynec.* **31** 806, 1936.

the gonadotropic and of the thyrotropic factors. The maximum dose was 50 rat units administered intramuscularly daily. This material was furnished by E. R. Squibb & Sons.

#### REPORT OF CASES

In general, the urine was normal in all cases except for minor abnormalities in case 4. The hemoglobin value, erythrocyte count, leukocyte count and differential count showed nothing abnormal except for a moderate decrease in polymorphonuclear cells in case 3. Roentgenograms of the chest revealed no lesion in any case (in case 4 roentgenograms were not made). Roentgenograms of the gastrointestinal tract in cases 1 to 5 were normal. The Kline test gave a negative reaction in each case.

**CASE 1**—A married woman aged 26 was admitted to the medical ward on June 8, 1933. The menses began at 11 years. There was a regular cycle of twenty-eight days, with a scanty flow lasting for two or three days. Since 1924, after the hazing incident to be referred to presently, menstruation had been irregular and painful, and the flow had diminished. In the spring of 1931, after appendectomy was done and one ovary was removed, the menses ceased altogether. She did not diet, but beginning in 1929, before her marriage in 1930, she became nervous, lost her appetite and grew thin. For the past two years she had lost weight and had reached the stage of emaciation.

A psychiatrist said of her in 1933: "While she is neurotic, in the sense of being intense, it does not appear that this is at the present time a leading feature."

Physical examination revealed no abnormality except extreme emaciation. The temperature was 36 to 37 C, the weight was 35 Kg (77 pounds), the height was 168 cm (66 inches) and the pulse rate averaged 70. The blood pressure was 98 systolic and 68 diastolic. The blood sugar values were as follows: during fasting, 67 mg, a half hour after dextrose was given, 165 mg, at one hour, 200 mg, and at two hours, 143 mg per hundred cubic centimeters. The basal metabolic rate was -15 per cent. Assay of the urine collected in twenty-four hours showed no estrogen. The vaginal smear made on June 26 showed characteristics of the atrophic postmenopausal type (fig. 1).

On June 12 I made the following note: "The emaciation and glandular disturbances suggest a possible deficiency of the anterior lobe. There are indications in the history of a psychoneurotic disturbance."

She was discharged from the hospital on July 25, the diagnosis being malnutrition and amenorrhea due to debility. Her progress is shown in the accompanying chart (fig. 2). While in the hospital, beginning June 8, she received 5 units of insulin three times daily before each meal. This gave her a voracious appetite. She also received injections of 10 rat units of an anterior pituitary extract containing the growth hormone daily, beginning June 24, for a long period. No vitamin supplement was ordered at any time. Coincident with the treatment she gained rapidly in weight, weighing 35 Kg at the start in June and 48 Kg in November, an increase of 13 Kg (29 pounds). The vaginal smears showed a change from the atrophic to the normal adult appearance, attaining the latter in October (fig. 1). In November regular menstruation was resumed for the first time in ten years. After a lapse of treatment during March, April and May the dose of the anterior pituitary extract was increased to 20 and 30 rat units daily, without any notable increase in weight beyond the level already attained. About



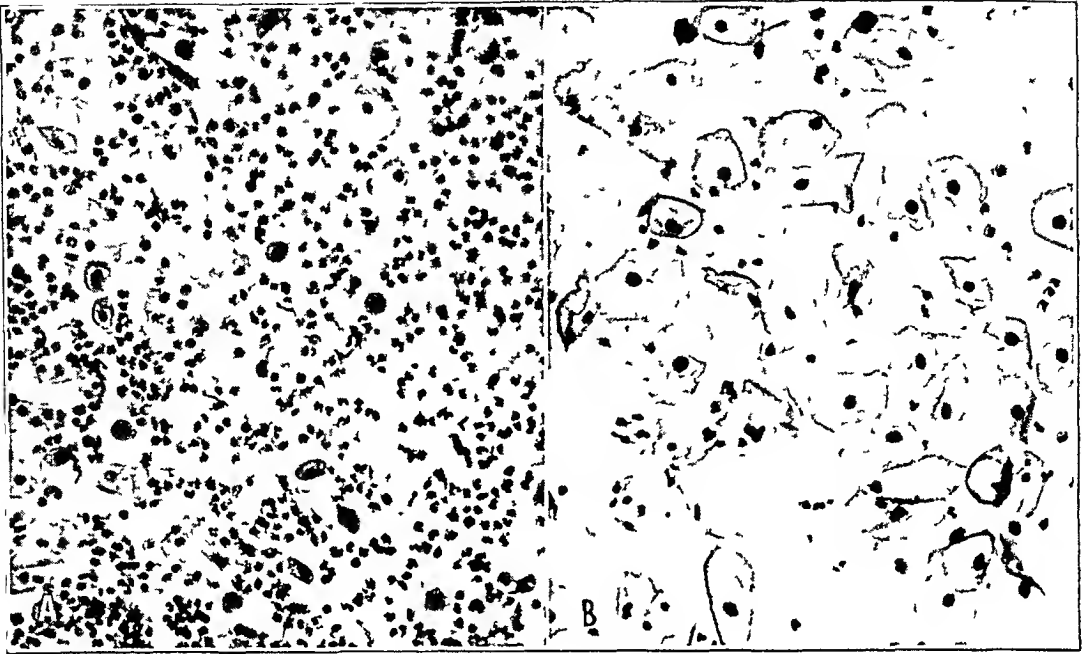


Fig 1 (case 1) —Anorexia nervosa A, the atrophic or menopausal type of smear obtained on June 26, 1933, at the height of the illness, showing a low level of ovarian function Note the small cells which come from the deeper layers and also the great numbers of leukocytes B, normal type of smear, obtained on October 20 Note the large cells and the relative scarcity of leukocytes Dr George N Papanicolaou gave permission for the use of these photomicrographs

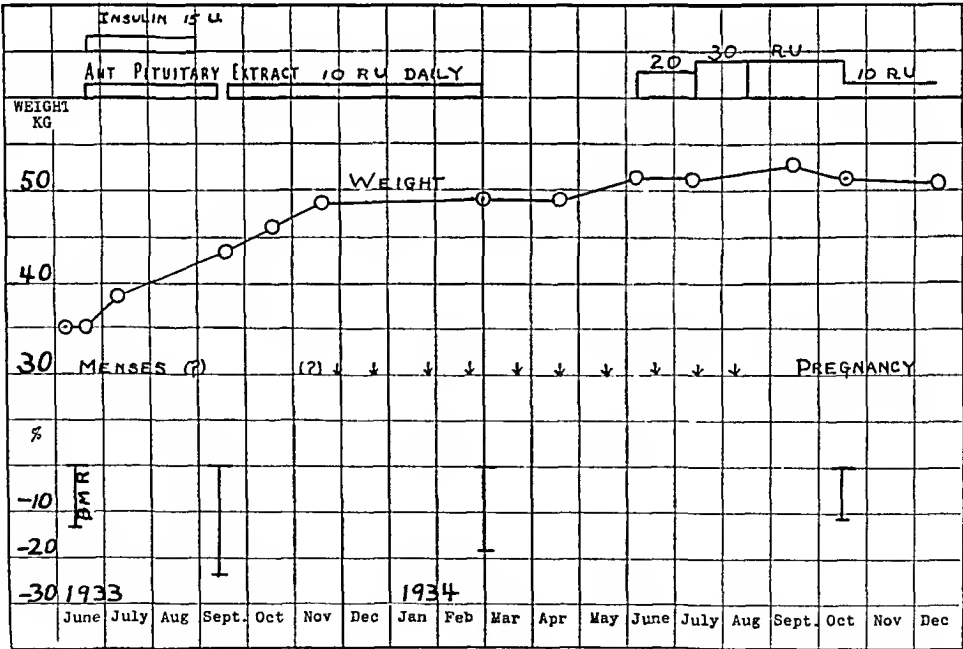


Fig 2 (case 1) —Anorexia nervosa Chart showing the course of the illness The menses are indicated by arrows The basal metabolic rates are shown by the length of the individual lines

this time her mother was taken to an institution for patients with mental disease. In August 1934 the patient's menstrual periods ceased. On June 3, 1935, she gave birth to a healthy girl, who weighed 6 pounds and 11½ ounces (3,050 Gm). In August the menses returned but were frequent and profuse. They became regular again in November, and the flow gradually decreased. The curve of the blood sugar tolerance returned to normal, the figures on March 17, 1937, being as follows: during fasting 81 mg, one-half hour after dextrose was given, 136 mg at one hour, 133 mg, at two hours, 83 mg, and at three hours, 60 mg per hundred cubic centimeters.

It was not until March 1937 that the whole picture of her illness was put together. As a young child she was not strong. Enuresis occurred until the age of 8, also nocturnal episodes in which she would awake to find herself lying under the bed. She was afraid of the dark. She and her mother "got on poorly." In school she was bashful and panicky when she had to recite. She was sensitive to slights. In 1924, at the age of 17, when a freshman in college, she was "hazed" and was awakened from a sound sleep by being dropped in cold water. She became nervous and found it hard to make minor decisions. She awoke at night, afraid that she was dying, but was unable to call out, then she would go to her mother for help. She began having dysmenorrhea and irregular periods.

She did not lose weight until the autumn of 1929, before her approaching marriage. Her mother refused to allow the fiance to come to the house. Her father approved of the marriage and arranged for it against the opposition of the mother. The patient became too nervous to eat and lost weight. After an operation in 1931 at which the appendix and one ovary were removed, she and her husband went to live with her mother. Once more they felt her antagonism. The situation was very difficult, and they moved later to a small apartment of their own.

Since 1932 the patient had been "terribly upset" by her mother's illness. The latter "went to pieces" in 1935 and had been confined in a hospital for patients with mental disease, where she died on June 11, 1937. The patient went through the stress at this time without any loss of weight, although she remained thin. Looking back on her mother's illness, she said she could trace its development, and she gained perspective on her mother's behavior in the past.

In March 1937 the injections of anterior pituitary extract were discontinued. On June 11 she stated that she had not felt better for fifteen years, she had been taking care of her child, who had been sick, and her husband, who was recovering from influenza, and felt well. On July 22 she weighed 45.6 Kg (100 pounds). She had received no injections. She continued to menstruate regularly every twenty-six days for four or five days. The flow was "not so intense," i. e., more normal.

*Comment*—This case fulfilled all the criteria of Simmonds' disease. The graph (fig. 2) of the patient's increase in weight and the onset of menstruation looks convincing as to the effect of pituitary extract, and the chief difficulty in interpretation appears to be the use of insulin during the first three weeks. The pregnancy and the birth of a normal child fulfil all the requirements for a return to endocrine balance. The psychiatrist did not consider in 1933 that her neurosis was a leading feature. Yet a review of her case in May 1937 led to the conclusion that the endocrine disturbance had nothing to do with her illness at

least as a primary factor. The loss of appetite and weight and the subsequent train of symptoms are to be interpreted as a neurotic reaction to an extremely difficult family situation.

CASE 2—A married woman, born in May 1898, was admitted to the medical ward on Feb. 20, 1933. The menses did not begin until she was almost 19 years old. They occurred every four or five weeks and lasted three or four days, and the flow was sparing. Often they ceased for three or four months at a time until her marriage. She gained in weight, and secondary sexual characteristics appeared at the age of 16 or 17 years. She was married in 1921, at the age of 23, and gave birth to children in 1923, 1926 and 1929. All three children were living and well. She was small at birth and had always been thin. She began to have headaches at the age of 23 and continued to have them except for interruptions in the two succeeding pregnancies. She had no postpartum infection and nursed her children six months. Since February 1931 there had been an extreme reduction in weight, from 124 to 68 pounds (56 to 31 Kg.), although her husband stated that she ate enough for three people. She noted frequent micturition, a falling out of the hair, the appearance of hair on the lips, chin, arms, lower part of the legs and forehead and spacing and punctate decay of the teeth. Formerly she had received satisfaction from marital relations, but there had been loss of libido and sterility for the preceding two years.

In October 1924 she first received injections, and she continued to have medical attention at frequent intervals, her condition usually being diagnosed as Simmonds' disease. At the New York Neurological Institute in 1933 she had an examination, and the spinal fluid was found normal. A diagnosis of a "psychoneurotic type of conversion hysteria" was made.

After a psychiatric consultation on March 3, 1933, Dr. Kirby wrote: "The patient has a personality disorder, the neurotic constitution being conditioned mainly by unfavorable parental and home influences (a domineering and suppressing mother). She has marked emotional instability and feelings of inferiority, with compensatory assertions and exaggerations and strong cravings for attention and praise. After the death of her mother (about 1920) there was an accentuation of the personality defects, and she reacted to illness and pain in a highly neurotic manner. Pituitary disease and a sacroiliac disorder now furnish avenues for marked neurotic display—magnification of symptoms (especially pains) and domination of family (husband) through invalidism and suffering."

Physical examination was made on Feb. 20, 1933. The patient appeared prematurely aged. She had a soft, thin skin, and the teeth were spaced and showed punctate atrophy. There was a high degree of general emaciation. The heart was small. There was hypertrichosis of the upper lip, chin, forearms and lower part of the legs. She weighed 37.8 Kg. (83 pounds) and was 159.5 cm. (63 inches) tall. The temperature was 36.2 to 37.2 C. (97 to 99 F.), and the pulse rate averaged 100. The blood pressure was 98 systolic and 70 diastolic. The basal metabolic rate was —4 per cent on March 2, 1933, and —13 per cent on Jan. 23, 1935. The lumbar portion of the spine showed a curvature. The vaginal smears made on April 21, 1933, were of an early postmenopausal type but without extreme atrophy. On Feb. 26, 1933, I made a note that this was a clear case of Simmonds' disease.

A high vitamin diet and injections of anterior pituitary extract were ordered, her subjective symptoms improved, but she did not gain in weight. She was discharged on May 8, 1933, the diagnosis being psychoneurosis. On September 29, largely at the insistence of the patient, the injections were renewed, 10 rat units being given three times a week at first and then more frequently until daily injec-

tions were being given by October 23. She made a rapid gain in weight, which did not reach its peak, however, until long after the treatment was discontinued (November 21). Discontinuance was carried out at first by substitution of saline solution for the active material in the original bottles until Feb 13, 1934. On March 13 she weighed 47.8 Kg, showing an increase of 10 Kg (22 pounds) since admission to the hospital. The injections were then discontinued altogether, and a precipitous loss of weight followed. Meanwhile she had three menstrual periods, beginning on January 2, February 8 and March 15, respectively. On March 15 the vaginal smear showed menstrual bleeding. Neither the weight nor the menstruation became normal thereafter, in spite of the use of anterior pituitary extract, from April to October 1934, up to five times the original dose. Other endocrine products, such as estradiol and estrone up to 1,000 rat units daily alone or in combination with gonadotropic substance from the urine of pregnant women up to 200 rat units, had no effect, apart from their subjective benefit. In October 1937 she weighed 36.2 Kg, which was less than she did on admission to the hospital. She had no further menstruation. At this time her husband described her violent outbursts of temper and her tendency to withdraw from social contacts. He also stated that at supper each day she would eat enough for two or three persons and then excuse herself, go to the bathroom and insist on privacy. He was certain that she vomited her meal at this time. Confirmatory evidence of this statement was the large intake of food before her first admission to the hospital, which contrasted with an ostensibly normal intake when she was in the ward under observation. Her fear of gaining weight was shown by her incessant and unnecessary activity, such as attention to summer clothes in the middle of winter. The use of her symptoms as a defense reaction came out clearly in her statement that if it had not been for her health she would have been "something besides a successful mother." The vomiting, of course, made it unnecessary to postulate Simmonds' disease as a cause of her illness.

*Comment*—A married woman of 35 years was admitted to the hospital in February 1933. She had evidence of antecedent ovarian insufficiency in the form of late, scanty and infrequent menstruation, but her sexual development was normal and she gave birth to three children. She was known to have a neurosis of long standing, based on parental influences, which led her to dominate her own family. She had all the clinical evidences of Simmonds' disease. Striking improvement and three normal menstrual periods followed the use of glandular injections, but the peak in weight came only after a long latent period and continued when a placebo was substituted. When the latter was also withdrawn, there was a precipitous loss of weight, and the menses again ceased. There was no further improvement when the dose was increased. The menses never returned, and she lost weight gradually, in spite of further replacement therapy, until October 1937, when she weighed less than on entry, 36.2 Kg as compared with 37.7 Kg. It was thought that she had organic insufficiency of the anterior lobe of the pituitary and that her neurosis improved as the result of the improvement in her physical condition. Subsequent events, particularly the discovery that she induced vomiting in order to keep down her weight, made the diagnosis of Simmonds' disease superfluous.

CASE 3—A girl was admitted to the medical ward on June 1, 1934, at the age of 16 years and 7 months. She was admitted at the request of Dr. Arthur Heyl, of New Rochelle, N. Y., excerpts from whose letter will be given presently. As a child she was chubby and at puberty short and overweight. She was strong and athletic during childhood. In the spring of 1930 she weighed 159 pounds (72 Kg.). In August of that year the menses began, at the age of 12¾ years. The cycle lasted for twenty-eight days and the flow for three or four days. This continued for nine months, until May 1931, when menstruation ceased, although she had not yet dieted and still had normal nutrition, as shown by a weight of 140 to 145 pounds (63.5 to 66 Kg.). In August 1931 she began to think of dieting. In December of the same year, at the age of 15 years, she fell from a horse and was unconscious or semiconscious for several hours. Roentgenograms of the skull, made at the New Rochelle Hospital, showed no fracture. In February 1932 she began to diet strenuously. In April she weighed 128 pounds (68 Kg.). In the summer she restricted her diet still more. In August 1932 she had a "menstrual show" for less than a day. In 1933 she continued to lose weight rapidly, weighing 88 pounds (40 Kg.) in January 1934. In June 1933 she received a prescription for estrogen and also for thyroid, the dose being unknown. In December 1933 she was observed at the New Rochelle Hospital. Roentgenograms of the chest and of the adrenal glands were normal, the tuberculin test gave a negative reaction. She was given a high caloric diet, also estrogen (estradiol), gonadotropic substance from the urine of pregnant women (antuitrin-S), bema-x (yeast), haliver oil with dicalcium phosphate, a high intake of salt and an extract of adrenal cortex (eschatin). Thyroid, 6 grains (0.39 Gm.) a day, only made her nervous. In January 1934 her basal metabolic rate was —34 per cent. In February 1934 she weighed 66 pounds (30 Kg.). She was given insulin for two days, after which she became apprehensive, was alternately hot and cold, perspired profusely and was said to have fainted. She had screaming tantrums. She was given dextrose by rectum, as she refused to take it by mouth. On February 23 she was taken to the New Rochelle Hospital, after having been hysterical all night. There she was given 8 ounces (240 cc.) of milk by forced feeding, and severe epigastric pain developed. At this time roentgenograms showed that her gastric and intestinal function was normal. She was "blind" for three days. In March 1934 the dextrose tolerance test gave normal results, 100 Gm. of dextrose being used. The spinal fluid was normal. The same month she received 10,000 rat units of estradiol (dihydroxyestrin) for six days and on April 1, 1 or 2 cc. of gonadotropic substance from the urine of pregnant women together with an estrogenic substance (estrone) two or three times a week. In May 1934 she was receiving an extract of adrenal cortex (eschatin), apparently in too small a dose, and had symptoms like those of an adrenal crisis—extreme nervousness, lassitude, complete failure of the appetite, dehydration to the point of acidosis, sharp aching in the epigastrium and almost complete anuria for twenty-four hours. With the injection of 25 cc. of the extract of adrenal cortex she felt much better and had a good night's sleep. The injections were continued.

As a child she was strong and outplayed her brother in athletics. She seemed to desire to excel in order to win a place in the family circle, since the oldest child was the only son and the youngest a "baby" girl. She was the "odd middle" child. She had a strong attachment for her mother and a "complex" against her father. As a child she was shy and moody with boys. She was a tomboy, boisterous and impulsive. She associated especially with one boy, with whom she played baseball, swam and generally "knocked about." She was "crazy mad"

about horses and liked "peppy" horses. She started dieting because she abhorred fat people and believed that no boy cares for a fat girl. She became intensely interested in diet kitchens and calories and developed a routine and ritual of eating. She began to smoke, swear and paint her lips and nails heavily, in general, adopting a "tough" attitude. At times she was hysterical. She withdrew from social contacts. She gave up meat early and acquired a strong sense of disgust for foods which she did not like. An item in the medical history was the development of a stomachache when food was forced on her. In the New York Hospital she was given one meal by tube at first, and three tube feedings were ordered. On the



Fig 3 (case 3) —Anorexia nervosa. Photograph (June 1934) showing the extremely advanced emaciation in the absence of morphologic changes in the pituitary body (see fig 4)

night before the latter order was put into effect she attempted suicide by scratching her wrist, first with a nail file and later with a piece of broken glass. The next morning she said that she had been cheating all along, that she had been disposing of the food and fluid without ingesting it and that she had been doing this at home also. The impression of the psychiatrist at this time was expressed as follows: "She is reacting in her immature, determined, childish way situationally, and it cannot be said that she is essentially depressed."

Opinion as to her status and its relation to the development of her symptoms was in doubt both when she was at home and after she came to the hospital. When

she was admitted to the New York Hospital I concurred in the opinion that the psychic disturbance was secondary to pituitary insufficiency. The question was settled only by autopsy.

On entry, on June 1, 1934, she complained of abdominal pain, and the nurse noted that the pain occurred after meals. Physical examination showed nothing except emaciation (fig 3). The temperature was 36.4 C (97.5 F), the height was 161 cm (5 feet and 3¼ inches), the weight was 28.8 Kg (63.5 pounds) and the blood pressure was 72 systolic and 54 diastolic. The blood sugar value was 103 mg per hundred cubic centimeters, and the basal metabolic rate was —40 per cent.

In the hospital there was no improvement in weight. She received 1 cc daily of the extract of adrenal cortex and sodium chloride by mouth up to 6 Gm. On June 11 she was given an anterior pituitary extract containing the growth hormone (Squibb), 5 rat units daily, increased on June 12 to 10 rat units, on June 13 to 20 rat units and on July 9 to 40 rat units daily. She was given 4 cc of extract of vitamin B (Parke, Davis & Co.) daily until June 19. Beginning June 28 she was given 4 cc of concentrated rice polishings daily, and beginning July 8, 4 cc of syrup of hydriodic acid daily. On June 22 she had symptoms of pyelonephritis and died on July 14, twelve hours after a transfusion of 100 cc of citrated blood.

Autopsy was performed six hours after death by Dr. Mitelfart. The uterus was somewhat small. The cervix was patent. The fimbriated ends of the tubes were open. The ovaries were somewhat smaller than usual. Their surface was white and slightly wrinkled, and on section numerous partially developed follicles were seen in both ovaries. The vagina was in no way unusual. Rugae were present, and the mucosa was not atrophic.

The ovaries (examined by Dr. Papanicolaou) appeared undeveloped. There was much fibrous tissue. Only one medium-sized follicle was seen, this was not close to the ovulation point. The epithelium was intact. Several primary oocytes were seen.

The thyroid gland was normal.

The pituitary body (examined by Dr. R. A. Moore) was normal (fig 4) except that the acidophils were small and poorly granulated. The basophils were present in the usual number and appeared normal.

No definite thymic tissue was seen.

*Anatomic Diagnosis*—The diagnosis was extreme malnutrition, bilateral pyelonephritis, cystitis, thrombosis of the left internal and common iliac veins, thrombosis of the cavernous sinuses, infarcts of the lungs, dilatation of the right ventricle, passive congestion of the liver, ascites, bilateral hydrothorax, edema of the lower extremities and purpura. Note was also made of slight lipoidosis of the aorta and a healed appendectomy wound.

*Comment*—A girl of 16 years was brought to the hospital in an advanced state of emaciation (fig 3). There was some indication of preceding ovarian insufficiency (amenorrhea) which preceded the loss of weight. The psychiatric history was incomplete, and the psychiatric opinion, expressed when she was in the hospital and elsewhere, was that a primary psychic disturbance was not the cause of the loss of weight. She had, in an exaggerated form, the symptoms often attributed to Simmonds' disease, and the diagnosis seemed clear, even to the point of the adrenal crises, which could be interpreted as the result of secondary adrenal insufficiency. At autopsy no lesions of the endocrine glands

could be detected (fig 4) This case is cited at length because the diagnosis of Simmonds' disease, which seemed obvious, was disproved at autopsy

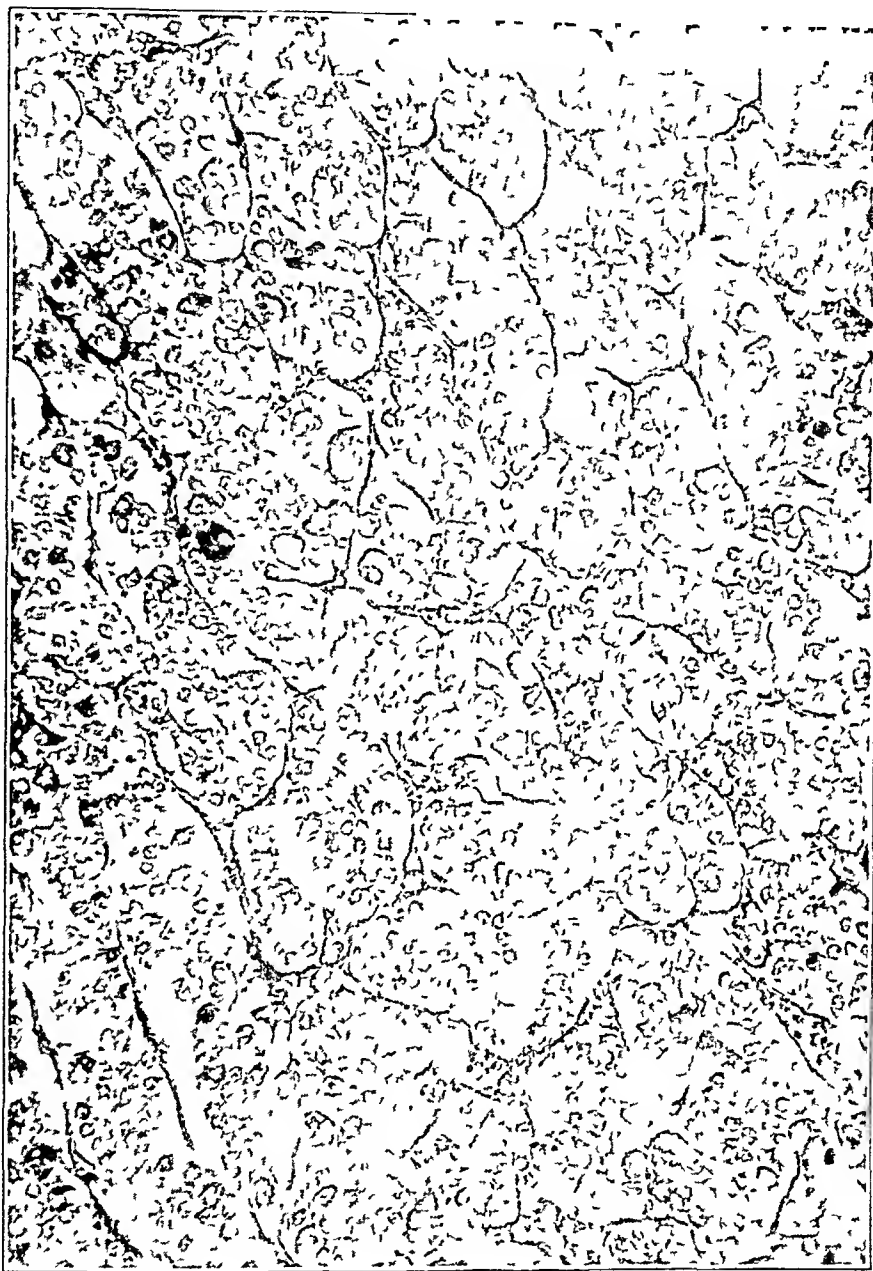


Fig 4 (case 3)—Anorexia nervosa A section from the anterior lobe of the pituitary body stained with Mallory's aniline blue and orange G stain,  $\times 175$

CASE 4—A girl aged 17 was admitted to the clinic on Oct 24, 1935 The menses began at the age of 13 years, with cycles of one month and a flow of three days At about 12 years she had an earache and was told that she had "mastoid trouble" but that an operation was not necessary The discharge from the ear continued for two weeks She said that since then whenever she had a cold the first place affected was the ears She had lost her appetite, and during the preceding year her weight had decreased from 145 to 120 pounds (66 to 54.5 Kg) In November 1934, a year previous, the menstrual flow became scant and in January 1935 it ceased altogether



In a psychiatric interview it became evident that the cause of her symptoms was her drunken, abusive and violent father, who had been associating with other women in a manner which brought embarrassment to the family

Physical examination was made on October 24. She was tall and rather thin. The roentgenographic appearance was typical of pansinusitis on the left. The vaginal smears made on October 24 were of the atrophic type. The temperature was 36 C (96.8 F), the pulse rate 68, the height 168 cm (5 feet and 6 inches), the weight 54.5 Kg (120 pounds) and the blood pressure 108 systolic and 82 diastolic. The urine contained a small and variable quantity of albumin, a few white blood cells and on one occasion many red blood cells. The basal metabolic rate varied from —25 to —30 per cent. The vaginal smears were of an atrophic type, indicating a low level of ovarian function but with evidence of a follicular reaction later, on Feb. 3, 1936, after she had received thyroid. Beginning Jan. 4, 1936, she was given 0.03 Gm (0.5 grain) of thyroid daily for a week, followed by 0.06 Gm daily for three weeks. This was continued, with an increase to 0.12 Gm daily on January 18 and to 0.18 Gm on February 15. Her weight fell from 54.5 Kg (120 pounds) on entry in October to 43.7 Kg (96 pounds) on February 29. The use of thyroid was discontinued on this date. While receiving it she lost 8.4 Kg. She was then given 10 rat units a day of anterior pituitary extract containing the growth hormone, receiving in all sixteen injections up to July 30. The vaginal smears were still of the atrophic type on July 23. By this time she had gained, weighing 46.5 Kg (102 pounds) but was still 8 Kg below her initial weight. She then stopped coming to the clinic and received no further treatment of any sort. Six months later, on Jan. 12, 1937, she returned to the clinic and was found to have regained the 8 Kg which she had lost since entry. She was feeling well and was eating and sleeping well.

On Sept. 7, 1937, her weight was 62.6 Kg. She said that the menses had never returned.

*Comment*—This girl reacted in a neurotic manner by loss of appetite and weight to an overt family situation, namely, drunkenness of the father. Her loss of weight became precipitous and alarming on the administration of thyroid. Anterior pituitary extract in small doses had no demonstrable effect. She left the clinic, discontinued treatment and regained her original weight and health.

CASE 5—The patient was admitted to the medical ward on March 2, 1936, at the age of 32 years. The menses began at the age of 16 years and were always irregular, occurring two to four times a year, lasting two to five days, with moderate to scanty flow. From the age of 5 to 8 years she had "running ears" every winter, with discharge and pain. At 14 she had chorea for five months. After this she gained weight rapidly. At 21 years she had an appendectomy for recurrent appendicitis. She weighed 8 pounds (3.6 Kg) at birth and was fat until the age of 7. From 7 to 14 she was as thin as on entry, and from 14 to 28 she was "pretty stout." At puberty, about 1920, she weighed 140 pounds (63.5 Kg), in 1926, 160 pounds (73 Kg), in 1933, 118 pounds (53.6 Kg), and in April 1935, 80 pounds (36.4 Kg).

In 1929, after she had been teaching school, work which she found difficult and uninteresting, she had anorexia. In 1933 she worked as a taster in a bakery and lost her appetite altogether, and her weight dropped to 118 pounds (54 Kg). She noted a gradual swelling of the body, including the face, and progressive loss

of strength. She took cathartics to the point of passing eight stools a day and had not had a formed movement in years. The basal metabolic rate at this time was —25 per cent. In April 1935 she showed progressive weakness, less edema and a loss of 15 pounds (6.8 Kg) more in weight. She then weighed 90 pounds (41 Kg). At this time she first complained of gaseous distention. In the summer she had a craving for fluids, gradual failing of strength, and weakness and dizziness relieved by walking. With a restricted diet the distention disappeared, but the edema continued. From December 1935 to February 1936 she again lost weight and strength, had cramps in the feet and began to have insomnia. She

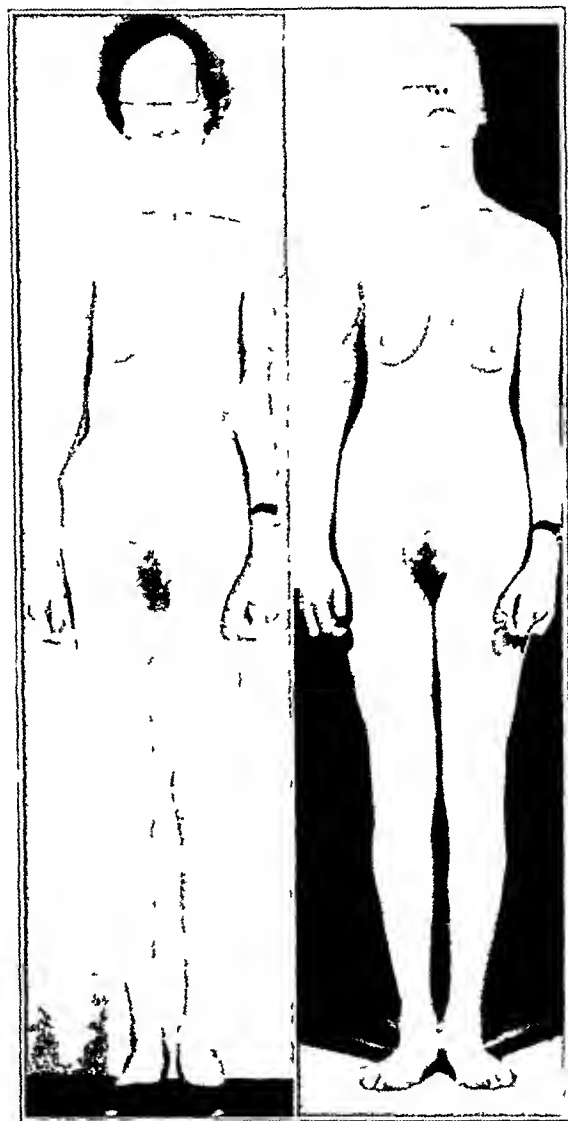


Fig 5 (case 5) —Anorexia nervosa. Left picture shows emaciation on March 6, 1936, right, a return to a normal state of nutrition on April 4. The treatment consisted solely of the giving of a high caloric diet, yeast and tomato juice.

had spells of weakness lasting three days at a time, about once every three weeks. She became restless, irritable and "low in her mind." She said that she never perspired.

At a psychiatric consultation it was found that the patient and her family concentrated on gastrointestinal functions. It appears that diet, constipation and laxatives had been one of the chief interests in the patient's life since childhood.

Other indications of her physiologic and emotional immaturity were found in the menstrual irregularities, her lack of sexual desire and her lack of interest in men. Her state of malnutrition seemed to be largely the outcome of her habits of living, especially in regard to diet and laxatives. She did not appear to be especially concerned about her condition and needed supervision for an indefinite period in regard to her general hygiene.

Physical examination, on March 2, 1936, showed emaciation (fig 5). The temperature was 35.4 C (95.8 F), the pulse rate 80, the height 170 cm (5 feet and 7 inches), the weight 38.4 Kg (84.5 pounds) and the blood pressure 100 systolic and 60 diastolic. The basal metabolic rate was —20 per cent. A vaginal smear showed a large number of leukocytes. It was of the atrophic type. *Trichomonas vaginalis* was present.

She was given no medical treatment except a high caloric diet, 4 Gm of brewers' yeast twice a day and 90 cc of tomato juice twice a day. She was discharged after five days. On April 4 she returned to the outpatient department. Her weight was 55.3 Kg (122 pounds), an increase of 17.3 Kg in thirty-three days. Obviously this increase was mostly due to fluid. The vaginal smear showed fewer leukocytes and was of an atrophic menopausal type. On April 28 her weight was 58.6 Kg (129 pounds), and the edema had continued. On May 26 her weight was the same, 58.9 Kg, but she was no longer edematous. The vaginal smear continued to be of the atrophic type as at the last examination in June 1936. In September 1936 she wrote that she was in excellent condition and weighed 132 pounds (60 Kg). On March 13, 1937, she wrote that her weight was 130 pounds (59 Kg) but that she had not menstruated. She said that she felt 100 per cent better than a year before but still not right. She continued to have swelling and puffiness off and on and a variety of nervous and gastrointestinal symptoms. Her intake of cathartics was still excessive.

*Comment*—This patient had loss of appetite, extreme restriction of the intake of food, to the point of a protein deficit, and amenorrhea. Menstruation started late. She had no interest in the opposite sex, and examination showed defective development or atrophy of the genital tract. Further evidence of an ovarian disturbance was the extremely infrequent menstruation, even when she was in good health, and the failure to resume menstruation after the inanition was relieved. She shared with her family a definite neurosis, with preoccupation regarding the gastrointestinal tract. She regained her normal weight (fig 5) and was able to resume active work, with no medication whatever. There was no treatment except a high caloric diet, vitamins and the injunction to eat.

CASE 6—A single woman aged 27½ years was admitted to the medical ward on Jan 13, 1937. Her father had had gastric ulcer for many years and had a gastroenterostomy at the age of 56 (in February 1936). The mother had a hemorrhage from a gastric ulcer at the age of 34 (in 1922) and died the following day. The patient was an only child. The menses started at 13 years. The cycle was three weeks long, with a duration of flow of four or five days. The flow was "quite heavy" before amenorrhea set in at 24 years. Before dieting she weighed 128 pounds (59 Kg). In January 1931 she began to diet, and at the end of a year and a half she had lost about 25 pounds (11 Kg). After that she

stopped menstruating When she reached her present weight she no longer tried to lose, and she had no desire to gain weight In fact, she said that she had a "complex" against gaining, that her state of malnutrition was as much a part of her as her right arm

She was observed at the Presbyterian Hospital in New York from Oct 18 to Nov 9, 1933 Her weight was 75½ pounds (34 Kg) The diagnosis was malnutrition, with secondary atrophy of all sex characteristics

The following is an abstract of a psychiatric consultation held at the Payne-Whitney Psychiatric Clinic on March 19, 1937 The patient dated her determination to lose weight back to a house party in January 1931, where she became interested in a medical student At that time some one made a remark about her plumpness She began to diet and reduced her weight from 128 to 110 pounds (58 to 50 Kg) in six months In the meantime she was carrying on a courtship, mainly by correspondence After she lost more weight the parents of the medical student became alarmed and suggested that she might have tuberculosis, and the affair gradually faded out At the same time she lost her job The dieting then seemed to change its role, being associated with a feeling of guilt, she felt that she should spend as little as possible for her food, as she was not supporting herself By the end of three years she weighed 75 pounds (34 Kg) She became more constipated Her friends noted that she lacked enthusiasm and zest and mingled less freely with people She accepted dinner invitations but always appeared after the meal, with some flimsy excuse Although she admitted carrying out a procedure (extreme dieting) that had attracted comment and caused concern, she also said, "I still feel that I look husky and stocky My relatives, I know, are in despair over me I went to the other extreme of being a beautiful martyr Sometimes I feel as if I were doing it for spite" The diagnosis was psychoneurosis with depression and starvation

Physical examination on Jan 13, 1937, revealed no abnormality except extreme emaciation, she appeared to be only skin and bones The eyes had a staring expression, which gave her a hunted or trapped appearance The temperature was 36 C (96.8 F), the pulse rate 76, the height 159 cm (5 feet and 3 inches), the weight 30.4 Kg (67 pounds) and the blood pressure 88 systolic and 52 diastolic On January 16 a dextrose tolerance test gave the following values for blood sugar during fasting, 51 mg per hundred cubic centimeters, one-half hour after dextrose was given, 59 mg, at one hour, 57 mg, at two hours, 48 mg, and at three hours, 27 mg The basal metabolic rate was -27 per cent The vaginal smears were typical of the atrophic postmenopausal state A calorimetric observation confirmed the low metabolism and revealed a respiratory quotient of 0.86, which was a little high as compared with the quotient for normal persons but within the normal range The most interesting observation made while she was in a ward for metabolic study concerned her behavior She was given a diet low in calories, but she resisted taking food by hiding it or vomited after eating She conversed about poisons and their relative merits and asked as to the presence of poisons in the ward This was taken as evidence of an interest in suicide She was admitted to the Payne Whitney Psychiatric Clinic on February 2 with a weight of 29.9 Kg For a long time both her physical and her mental condition remained stationary It became evident that the emaciation was part of a highly organized neurosis which had its roots in her childhood This served as a protective mechanism against the adoption of an adult reaction to her development as a woman and her position in the economic and social life Excerpts in support of these statements are as follows "I was very close to my mother I was the only child, as a child I was afraid that my father and mother would separate

I had feelings of inadequacy at an early age I was a somber child It really started when I was very young I feel a little like David Copperfield, I am always going to do something wrong and get my hand slapped" The mother and father quarreled continually over money She said of her lack of confidence in herself that she grew up with it "My mother was a wonderful person as a mother She wanted me to be perfect She disparaged what I did I grew up with feelings about myself I compared myself with other children I wanted to be dignified and respected I feel the old inhibitions are just the same The less enjoyment I get, the happier I feel Ten years ago streaks of depression were there I went from high to low I was always insecure" She had periods of depression during her last year in college, felt inadequate socially and was unhappy among the group of girls that she met there She said that she was afraid to face a career because she was afraid of failure "I seemed to enjoy being a martyr I don't know how I could have punished myself more unless I had stuck thorns into myself No one was going to hire me for a job looking as I did"

By May 7 she had gained 15 Kg On June 17 she was given cod liver oil, 1 tablet three times a day, increased to 2 tablets three times a day, until July 12 Tube feedings were suggested but were not given About July 10 it was also suggested that her progress was so slow that she might have to leave the institution From July 11 to 23, inclusive, 2,000 rat units of estrogen (estradiol) was given daily intramuscularly Vaginal smears showed a definite improvement, with a more normal appearance On July 12 tablets containing vitamins A, B and D were given three times a day The weight on July 31 was 32.9 Kg On July 20 use of yeast concentrate was started, and tube feedings were again discussed She said that she would leave the clinic if they were started From August 14 to 23 injections of estradiol were given 3,000 rat units, increased to 5,000 rat units, daily (a total of 40,000 rat units being given) This produced a definite follicular reaction, as noted in the vaginal smears On August 30 the weight was 35.6 Kg From August 29 to September 4 there was vaginal bleeding as a result of the injections but no menstruation Blood sugar determinations were as follows during fasting, 78 mg, one-half hour after dextrose, 174 mg, at one hour, 118 mg, at two hours, 94 mg, and at three hours, 115 mg per hundred cubic centimeters From September 9 to 23, 4,000 rat units of estradiol was given daily

On October 7 she expressed herself as feeling better than at any other time in her life The appearance of her face had changed so much that she could scarcely have been recognized from her photograph taken in January The hunted expression was gone, and her face was placid The pulse rate was 84, the blood pressure 86 systolic and 62 diastolic and the weight 38.2 Kg (84 pounds) There was no evidence of spontaneous menstruation up to October 22

*Comment*—This patient presented in detail the clinical picture of Simmonds' disease, although there was nothing to support this diagnosis On the other hand a psychiatric study revealed a profound neurosis with origin in childhood Her behavior resembled closely that of one of the other patients (case 3), whose endocrine glands were normal at autopsy She improved markedly, with a gain in weight of 8.6 Kg (19 pounds), after psychiatric treatment combined with the use of estrogen and a vitamin supplement

## COMMENT

This work was undertaken as a clinical study of insufficiency of the anterior lobe of the hypophysis in adults with an attempt to demonstrate the effect of replacement therapy. With study of the first patient of the series it became evident that the distinction between Simmonds' disease, or organic insufficiency of the pituitary gland, and anorexia nervosa is difficult to make. The first 3 patients were all thought at some time to have Simmonds' disease. In the first case this was rendered improbable in the course of time by the unfolding of a history of a neurotic reaction to a difficult family situation. The second case became clarified when it was found that the patient induced vomiting to keep down her weight. The diagnosis in the third case (fig 3) remained obscure until autopsy, when it was demonstrated that there was no lesion of the endocrine glands (fig 4). Three other patients were included, although the predominant psychic factor was obvious, because the symptoms, physical signs and laboratory data were exact counterparts of the findings in Simmonds' disease. Case 4 was also interesting in that thyroid had a dramatic and harmful effect, with the loss of 8.4 Kg, and spontaneous cure was obtained while the patient was absent from the clinic, without any medication whatever. The fifth patient returned to normal nutrition and physical health (fig 5) on the simple admonition to eat. The sixth patient was found by psychiatric observation to have a profound, highly organized neurosis with its origin in childhood. She presented a condition analogous to that of the third patient, in whom no lesion of the endocrine system could be found at autopsy. Two other patients have been observed more recently, but their data are not included in this paper.

Thus, all our patients were found to have anorexia nervosa. In four years no instance of Simmonds' disease was encountered, in spite of special interest in it. This is an indication of the rarity of the disease, which has already been shown by Silver<sup>3</sup> (1933), who was able to collect autopsy reports of only 41 cases which had been published over a period of nineteen years. Frazier<sup>11</sup> (1929) has stated that it is rare even in cases of destructive lesions of the pituitary body.

The comparison of the symptoms presented by our patients with those reported in cases of Simmonds' disease in which the diagnosis was confirmed by autopsy shows a close similarity. Most of the features of the disease which bears Simmonds' name were pointed out by him<sup>1, 2</sup> (1914, 1916 and 1918). The clinical data tabulated by Silver<sup>3</sup> (1933) in a review of the proved cases are as follows. The great majority of the patients were women. Only 10 proved cases had been reported

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11 Frazier, C. H. Pituitary Cachexia, *Arch Neurol & Psychiat* **21** 1 (Jan) 1929

in males Of 41 patients, 7 were below the age of 30, 21 were above the age of 39 and 11 were between 30 and 39 years of age The number of pregnancies was reported in 12 cases and averaged 5.7 Besides amenorrhea and cachexia, Silver listed asthenia, premature aging, genital atrophy, loss of libido, loss of pubic and axillary hair, atrophy of the jaw, loss of teeth, hypotension, hypothermia and eosinophilia Pathologic study showed that in 26 cases atrophy and fibrosis of the anterior lobe of the hypophysis were present Tumors, cysts, tuberculosis, syphilis or trauma was the causative factor in the other cases

It is obvious, without further discussion, that many of these symptoms can be caused by malnutrition The emaciation produces a loss of body tissue and of secondary sexual characteristics which gives the appearance of age, and the wrinkled skin accentuates this The trophic changes in the skin, hair and nails might be due to malnutrition or to vitamin deficiency The depression of the basal metabolism is a well known factor of conservation, as has been pointed out by Lusk The slow pulse rate and probably the low blood pressure are corollaries of this Malnutrition was found in studies of famine by Cornish<sup>12</sup> (1879) to cause "an impairment or abolition of the menstrual function"

Certain general features of our cases of anorexia nervosa may first be mentioned The family history was of no interest except with respect to a psychosis in case 1 and marked neurotic traits in cases 2 and 5 The patients were all women, and the ages were 26, 35, 16½, 17, 32 and 28 years, respectively Two of the patients were married The first patient had 3 children before her illness, and the second patient had a child after her recovery Neither had any evidence of puerperal infection The previous diseases were of no importance One patient had mumps, another had otitis media and a third had both of these diseases No evidence of chronic infection or neoplasm was found, although 5 of the 6 patients were extensively studied in the hospital The serologic reactions to tests for syphilis were negative in each case Roentgenograms of the skull and sella turcica and examination of the fundi and optic fields failed to reveal an expanding lesion of the pituitary body in any instance As outlined so far, the chief point of interest is the absence of repeated pregnancies and of puerperal infection or other diseases which are common in known cases of Simmonds' disease

The weights, compared with the normal averages with respect to age and sex (tables of the Metropolitan Life Insurance Company), were 63, 57, 53, 75, 59 and 58 per cent, respectively, of normal The appearance of age depended much on the extent to which the emaciation affected the face It was marked in cases 2, 3 and 6 Roentgenograms showed a small vertical heart in all cases except case 4 In cases 1, 3 and 5 the

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12 Cornish, cited by Sheldon<sup>13</sup>

patient was hyposthenic and in case 4 the opposite. Ptosis of the viscera and gastrointestinal tract was demonstrated in cases 1 and 5. A decrease in the size of the organs was noted on physical examination in case 2. This change has been given the name *splanchnomicia* but appears to have no necessary significance except as part of the emaciation. In case 2 spacing and atrophy of the teeth as well as changes in the nails were noted.

Amenorrhea was present in all instances. In some cases menstrual disturbance preceded the loss of weight, as noted in the case histories. In case 1 there was loss of libido from fatigue and in case 2 a definite loss. An increase in the amount of body hair was noted in these 2 cases. Pelvic examinations gave evidence of small internal genitalia in all cases except case 1, in which the fundus was normal. Regarding case 2 no information is available. Examination of the vaginal smears showed the type which is normally seen after the menopause (fig 1). The only exception was in case 3, in which a normal smear was reported. In case 4 the smear was atrophic throughout except for a follicular reaction on one occasion after thyroid was given.

The basal metabolism was low in all cases. The depression was not marked in case 1 (—15 per cent) or in case 2 (—8 to —17 per cent). The rates in the other cases were —40, —30, —20 and —30, respectively. The pulse rate was not especially slow except in cases 3 and 4, in which it averaged 65 and 68, respectively. The blood pressure was about 100 systolic, except in cases 3 and 6, in which it was conspicuously low —76 systolic and 50 diastolic, and 66 systolic and 32 diastolic. The cholesterol value was normal. Some of the patients had a variable amount of creatine in the urine. There was no eosinophilia in any case. The sugar tolerance test revealed a diabetic curve in case 1, a normal curve in cases 2 to 4 and a low flat curve in case 6. In cases 1 and 6 the values reverted to normal after an improvement in health. Instances of a flat sugar curve which reverted to normal on recovery have been reported by Sheldon<sup>13</sup> (1937).

It will be seen that these cases of malnutrition of psychic origin are scarcely distinguishable from known cases of Simmonds' disease. A similar statement has been made by Sheldon<sup>13</sup> (1937). The complete picture of Simmonds' disease was present in case 3, yet the absence of morphologic changes in the pituitary body was shown at autopsy (fig 4). The situation is further complicated by the fact that total destruction of the anterior lobe has been reported at autopsy in patients who had no signs of pituitary insufficiency. Krumbhaar<sup>14</sup> (1921) reported such

13 Sheldon, J. H. *Lancet* **1** 369, 1937.

14 Krumbhaar, E. B. *M. Clin. North America* **5** 927, 1921.



cases and cited others Kaminski<sup>15</sup> (1933) reported a case. The diagnosis can be made when there is evidence of an expanding lesion of the pituitary body, but this is uncommon (Silver,<sup>3</sup> 1933). Apart from the erosion of the sella turcica or the symptoms of diabetes insipidus, the chief clue is age. The expanding lesions are those which are more common in middle age, and repeated pregnancies are obviously impossible early in life. A history of puerperal infection is etiologic evidence, according to Simmonds<sup>1</sup> (1914), but this has been contested by Kaminski<sup>15</sup> (1933). When the patient is a young single woman with no demonstrable lesions, the diagnosis is particularly insecure. In the words of Gull,<sup>16</sup> young women "are especially obnoxious (susceptible) to mental perversity."

It is to be remembered, however, that repeated pregnancies are no guarantee against a psychic disturbance. For instance, Reye<sup>17</sup> (1926 and 1928) reported on patients who had symptoms of depression after childbirth. In such cases the possibility that the symptoms develop as the result of the psychosis, without any necessary change in the pituitary body, is not excluded.

If recovery takes place as the result of treatment with preparations of the anterior lobe, this is evidence of an insufficiency of the pituitary body. The use of the therapeutic test is implicit in much of the literature or definitely expressed, as by Reye<sup>17a</sup> (1926), von Bergmann<sup>18</sup> (1934) and May and Robert<sup>19</sup> (1935). Reports have been made of a large number of cases in which a diagnosis of Simmonds' disease, or hypophysial cachexia, was made and in which recovery occurred. Cases 1 and 2 of our series are closely analogous to these, apart from the diagnosis. In the literature the recoveries have often been attributed to the extracts which were used. There appears to be no justification for this. The effect of suggestion was not controlled, and the powerful psychic effect of a hospital regimen was not discussed. In many cases a variety of remedies was used besides the endocrine products. The effectiveness of whole gland by mouth has been reported by Reye<sup>17a</sup> (1926), Steinitz (1932), Kaminski<sup>15</sup> (1933) and others, although Smith<sup>20</sup> (1927) could obtain no effect by having hypophysectomized rats ingest large quantities. Many endocrine products have been reported as successfully used, including insulin (May and Layan,<sup>21</sup> 1929, and Zondek and

15 Kaminski, J. *Frankfurt Ztschr f Path* **45** 290, 1933.

16 Gull, W. *Tr Clin Soc London* **7** 22, 1874.

17 Reye (a) *Munchen med Wchnschr* **73** 902, 1926, (b) *Deutsche med Wchnschr* **54** 696, 1928.

18 von Bergmann, G. *Deutsche med Wchnschr* **60** 123, 1934.

19 May, E., and Robert, P. *Ann de méd* **38** 317, 1935.

20 Smith, P. E. *Am J Physiol* **81** 20, 1927.

21 May, E., and Layan, F. *Bull et mem Soc med d hop de Paris* **53** 302, 1929.

Koehler,<sup>22</sup> 1928) and extracts of the anterior lobe of the pituitary, the gonadotropic principle of the urine of pregnant women and estrogens Kalk<sup>23</sup> (1934) has also reported the successful use of adrenal cortical extract. The increase in weight is often slow during treatment and extraordinarily rapid after it is discontinued (May and Robert,<sup>19</sup> 1935, and von Bergmann,<sup>18</sup> 1934). According to several reports the patient continued in good health after the cessation of treatment (Calder,<sup>24</sup> 1932, Hawkinson,<sup>25</sup> 1935, Hurthle,<sup>26</sup> 1932, and May and Robert,<sup>19</sup> 1935). This contrasts with the results of treatment, with other endocrine products which are known to be potent, for example insulin and thyroid. The suspicion is that when replacement therapy of short duration is followed by permanent cure, the same effect might have been achieved with tablets of lactose or with injections of saline solution.

On the other hand, cases are reported in which the treatment had no effect. This was true of the patient reported on by Moehlig<sup>27</sup> (1936), who received, in addition to insulin, extract of adrenal cortex (eschatin), and 100 rat units daily to a total of 1,800 rat units of gonadotropic substance from the urine of pregnant women. The patient reported on by Regester and Cuttle<sup>5</sup> (1937) did not improve with the use of anterior pituitary extracts containing the growth hormone, 50 rat units every other day, increasing to a maximum of 250 rat units for seven injections. These doses are several times as large as those which are reported elsewhere as successful.

No therapeutic test is convincing unless the remedy is known to be efficient. So far no definite effect has been encountered in a proved case of Simmonds' disease. A partial exception is the patient reported on by Shelton, Cavanaugh and Patek<sup>28</sup> (1936), who gained 15 pounds (6.8 Kg) in weight without a change in basal metabolism or blood pressure. The same statement applies to hypogonadal dwarfs of adult chronologic age. In these cases the diagnosis of pituitary insufficiency may be regarded as established, since two of the functions of the pituitary body were lacking. Even in such cases it may happen that no striking lesion of the anterior lobe can be demonstrated at autopsy (Struck and

22 Zondek, H., and Koehler, G. *Deutsche med Wchnschr* **54** 1955, 1928

23 Kalk, H. *Deutsche med Wchnschr* **60** 893, 1934

24 Calder, R. M. *Bull Johns Hopkins Hosp* **50** 87, 1932, Pituitary Cachexia (Simmonds' Disease) Treated with Anterior Pituitary Extract, *J A M A* **98** 314 (Jan 23) 1932

25 Hawkinson, L. F. Simmonds' Disease (Pituitary Cachexia) Report of Case in Which Patient Responded to the Anterior Pituitary-Like Principle of Pregnancy Urine, *J A M A* **105** 20 (July 6) 1935

26 Hurthle, R. *Med Klin* **28** 1637, 1932

27 Moehlig, R. C. *Endocrinology* **20** 155, 1936

28 Shelton, E. K., Cavanaugh, L. A., and Patek, P. R. *Endocrinology* **20** 846, 1936

Szurek,<sup>29</sup> 1937) In this group the results reported by Turner<sup>30</sup> (1935) and Goldberg<sup>31</sup> (1936) are perhaps the most encouraging, but even with these the possibility of spontaneous development comes to mind Otherwise, no instance has been encountered in the recent American literature (Engelbach,<sup>32</sup> 1933 and 1934, Shelton, Cavanaugh and Evans,<sup>33</sup> 1934, and Schaefer,<sup>34</sup> 1936) of an unmistakable increase of height as the result of injections in the type of case mentioned In 6 adult dwarfs (unpublished data) I could demonstrate no effect either on height or on ovarian function as shown by vaginal smears

The explanation of this failure might lie in the fact that the disease is of many years' duration as compared with that in experimental animals In other words, irreversible changes might have taken place It seems more probable, however, that the doses have been too small The maximum of 100 rat units used for our dwarfs may be compared with doses of other hormones, for instance, the average of 500 to 2,000 rat units daily of estrogen necessary to produce objective changes in women with ovarian insufficiency (Papanicolaou and Shorr,<sup>10</sup> 1936) By analogy it may be reasoned that the unit for human beings is about 1,000 rat units, as compared to the maximum of 100 rat units used for our series of dwarfs and 50 for our patients with anorexia nervosa In the cases reported in the literature in which health was restored the dose was usually 1 to 2 cc of extract of the anterior lobe of the hypophysis, presumably 10 to 20 rat units

The therapeutic test as reported in the literature is unreliable for one or more of the reasons given, namely, (1) too many remedies were used simultaneously, (2) the factor of suggestion was not controlled, (3) the improvement was not parallel with the use of the medication, (4) the improvement persisted or even increased when the medication was discontinued and (5) the usual dose was altogether inadequate

Anorexia nervosa is diagnosed by the demonstration of the neurosis This is difficult, even if the examiner is interested in the inquiry, which is not always the case The demonstration is conclusive if the neurosis can be treated successfully by psychotherapy This, of course, is the application of a therapeutic test It is conclusive because psychotherapy can be given without medication, but it is impossible to give injections without psychotherapy When improvement occurs as the result of

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29 Struck, H C, and Szurek, S A *Endocrinology* **21** 387, 1937

30 Turner, H H *South M J* **28** 309, 1935

31 Goldberg, M M *Endocrinology* **20** 854, 1936

32 Engelbach, W, Schaefer, R L, and Brosius, W L *Endocrinology* **17** 250, 1933

33 Shelton, E K, Cavanaugh, L A, and Evans, H M *Hypophyseal Infantilism Treatment with Anterior Hypophyseal Extract, Preliminary Study*, *Am J Dis Child* **47** 719 (April) 1934

34 Schaefer, R L *Endocrinology* **20** 64, 1936

increasing the diet, whether by admonition or suggestion or by the injection of insulin, the probability is that the inanition is due to psychic influences rather than to pituitary insufficiency

In the diagnosis of Simmonds' disease as reported in the literature the psychic symptoms have received little attention. Yet they are not infrequently mentioned, and this leads to the inference that in many cases they are the predominant cause of the illness. Silver (1933) stated that mental disturbances are marked and may become the dominant clinical feature. Lang<sup>35</sup> (1924) described a patient with progressive changes in the direction of a Kotsakoff syndrome with the clinical picture of Simmonds' disease, but with a pituitary gland which was grossly and microscopically normal at autopsy. Reye<sup>17</sup> (1926 and 1928) described mental deterioration in 4 patients, none of whom were cachectic or had objective evidence of pituitary lesions. Redlich<sup>36</sup> (1927) gave a full description of the more profound disturbances occurring in hypophysial cachexia. Bickel<sup>37</sup> (1934) described the psychoneurotic symptoms in the sort of case which is discussed by the English school under the term *anorexia nervosa*. Von Bergmann classified this disease under the designation *Magersucht*. He described in some detail the psychic disturbances encountered by him in young girls. Besides the unwholesomeness of behavior, he mentioned persistence of infantile traits, as pointed out by Kalk, dependence on the mother and an interest in fairy tales. He related anecdotes in support of this statement. For instance, a man of 27 insisted that his mother should be present when he defecated. Von Bergmann also stressed the symptoms of obstipation and of pain in the epigastrium, which in the past often led to operation, always with normal findings. Roentgen examination in his cases revealed no abnormality. May and Robert<sup>19</sup> (1935) in a long article devoted a paragraph to psychic factors. Wahlberg<sup>38</sup> (1936) stated that 1 of his patients was considered by Josefson to have psychogenic *anorexia*. Rothmann's<sup>39</sup> (1935) patient, formerly in good health, wanted to become as slim as possible. She reduced and was pleased at the loss of each kilogram. This reduction was carried on in an exaggerated way and resulted in an uncontrollable loss of weight, leading to cessation of the menses. She was cachectic when first seen. She had an aversion to all edible substances and had chronic constipation, for which she made extreme use of cathartics. This history will recall our cases 3 and 6—cases of *anorexia nervosa*. In a detailed article Regester and Cuttle<sup>5</sup>

35 Lang, F. J. *Wien klin Wchnschr* **37** 917, 1924

36 Redlich, E. *Jahrb f Psychiat u Neurol* **45** 276, 1927

37 Bickel, G. *Gaz méd de France*, June 15, 1934, p. 535

38 Wahlberg, J. *Hypophyseothyrogenic Adiposity and Emaciation* *J. A. M. A.* **106** 1968 (June 6) 1936

39 Rothmann, H. *Acta med Scandinav* **87** 168, 1935

(1937) stated that a psychiatric study revealed nothing abnormal. Yet the patient first became nervous, acquired bad eating habits and then had a period of nausea and vomiting and severe abdominal pain. These symptoms became worse when her parents died, changing her economic status from one of comparative ease to almost poverty. Here was an overt situation which might well have intensified an emotional disturbance.

The incidence of psychic disturbances in cases of true Simmonds' disease, as distinguished from those in which the diagnosis cannot be verified, is hard to determine. Redlich<sup>36</sup> (1927) reported the development of a psychosis in a patient who had an eroded sella turcica and pupillary changes but showed a negative reaction to the Wassermann test of the blood. Howard and Rhea<sup>4</sup> (1936) described the late development of psychotic symptoms in a patient with a suprasellar cyst. Farquharson and Graham<sup>40</sup> (1931) reported 3 cases in which there was profound mental deterioration.

These references suffice to show the need of a psychiatric investigation in the diagnosis of Simmonds' disease. As indicated, the mere presence of a psychic disturbance is no proof that it is the dominating factor. In spite of the difficulties in interpretation, however, its occurrence in an emaciated patient should cause a scrutiny of the diagnosis. On the other hand, a predominantly psychic disturbance is entirely compatible with some degree of insufficiency of the pituitary body. This might antedate the malnutrition or might occur as a result of it. Evidence of ovarian insufficiency which antedated the illness was present in 3 of our cases (cases 2, 3 and 5). In addition, in cases 4 and 5 the patient failed to menstruate even after the nutrition and physical health had returned to normal. The ovarian disturbance might have originated in the ovaries or in the pituitary body. Sheldon<sup>13</sup> (1937) studied 5 patients with anorexia nervosa, in 2 of whom he found clear evidence and in 2 more presumptive evidence of a pituitary defect. He cited the menstrual history as recorded in the literature and after an admirable discussion stated as his conclusion, in agreement with Ryle's<sup>9</sup> (1936), that the "amenorrhea is an hysterical or functional symptom that develops independently of, or parallel to, the anorexia."

Von Bergmann<sup>18</sup> (1934) also discussed this question, but from the standpoint of hypophysial cachexia, and reached the opposite conclusion, namely, that the psychic disturbances are conditioned by biologic events. This is also a tenable position, but it appears to be based mainly on the therapeutic test, which has just been criticized.

Turning to the treatment of anorexia nervosa, we found in our series no evidence of any effect of extract of the anterior lobe of the

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40 Farquharson, R. F., and Graham, D. *Tr. A. Am. Physicians* **46** 150, 1931

hypophysis by intramuscular injections in doses up to 50 iat units daily. The giving of larger doses was prohibited by the development of severe local reactions. Thyroid was given in 1 of our cases (case 4) and was associated with an alarming loss of weight. Patients who received the extract elsewhere experienced no effect other than toxic symptoms (cases 3 and 5). In cases in which a diagnosis of Simmonds' disease was made Wahlberg<sup>41</sup> (1935 and 1936) claimed excellent effects, but Farquharson and Giam<sup>40</sup> (1931), Caldei<sup>21</sup> (1932), Riecker and Curtis<sup>42</sup> (1932), Hawkinson<sup>25</sup> (1935) and Rose and Weinstein<sup>43</sup> (1936) were unable to produce any benefit.

Insulin was given to only the first patient. It gave her a voracious appetite which apparently initiated her recovery. The third patient received it elsewhere, without effect except for attacks which might be interpreted as due to hysteria or hypoglycemia. Many patients have a flat blood sugar curve at a low level, as did our sixth patient and another not here reported on. Sheldon<sup>13</sup> (1937) reported 2 such cases. The patients would obviously be susceptible to insulin shock, as in so-called Simmonds' disease (Herman,<sup>44</sup> 1928, and Lucke,<sup>45</sup> 1932).

None of our patients had clinical evidences of vitamin insufficiency. This is surprising in view of the extreme state of caloric undernutrition. Five of the 6 received vitamin supplement in some form in addition to the vitamin content of the diet. In case 6 the patient received supplement for vitamin A, B complex, C and D. No inferences could be drawn as to the effect of this treatment beyond the statement that the first patient, who received no supplement, made the most dramatic and complete recovery. No report of this treatment by itself has been encountered in the literature.

The psychologic aspects of the treatment have been described by Langdon Brown<sup>46</sup> (1931) and others of the English school of "individual psychologists." An attempt to review the psychiatric literature would be out of place here. One question, however, has forced itself on our attention in 2 of our cases, namely, the extent to which the intake of food should be forced. Lasègue,<sup>8</sup> in 1873, described vividly the manner in which this may confirm and intensify the neurosis. The use of coercive measures rests, however, on good medical authority. Gull stated that "the inclination of the patient must be in no way con-

41 Wahlberg, J. *Acta med Scandinav* **84** 550, 1935, footnote 38.

42 Riecker, H. H., and Curtis, A. C. Hypophyseal Cachexia (Simmonds Disease), with Report of Three Cases, *J A M A* **99** 110 (July 9) 1932.

43 Rose, E., and Weinstein, G. *Endocrinology* **20** 149, 1936.

44 Herman, K. *Rev franç d'endocrinol* **6** 301, 1928.

45 Lucke, H. *Klin Wchnschr* **11** 1678, 1932.

46 Brown, W. L., and others. *Anorexia Nervosa*, London, C. W. Daniel Co., 1931.

sulted" He did not mention feeding with a stomach tube, which was a recent invention Ryle<sup>9</sup> (1936) included firmness as a part of the treatment in addition to assurance, removal from home and tact Apparently he did not contemplate any forcible measures, for he said, "In some cases it may be necessary to sit with the patient until each meal is finished" The fatal case reported by Stephens<sup>47</sup> (1895) does not inspire confidence in the use of coercion The third patient in our series was given one tube feeding a day, and it was planned to increase the number to three The night before this increase was put into effect she made two attempts at suicide Previously she had complained of abdominal pain when food was forced on her In case 6 the use of even the mild suasion which is customary in a ward where metabolic studies are made was distressing to the patient At first she hid part of the food, and when this was discovered she began to vomit At this time she evinced mild suicidal tendencies

Thus, the experience in our series indicates that forcible feeding or even persuasion may be dangerous In general, the attempt to break down a neurotic defense mechanism against the will of the patient is not without risk Admonition may be successful in the case of milder disorders, as it was in our case 5 Tube feeding may be unavoidable when starvation is severe enough to threaten life, but it should be undertaken with precaution and a realization of the risk It is best done under psychiatric guidance

To attempt in these cases to increase the intake of food by direct means is symptomatic treatment If it is desired to attack the cause, it is necessary to treat the neurosis, in other words, to employ psychiatric treatment or psychotherapy, if the latter term is preferred Obvious though this statement may appear, it is contested by medical authorities Von Bergmann<sup>18</sup> (1934), who clearly recognized the psychic aspects in his cases, would not go so far as to employ psychotherapeutic treatment Apparently he based his objection on the success of replacement therapy, although in the case which he emphasized in his discussion the patient died and even the glandular treatment failed Ryle<sup>9</sup> (1936) stated that psychoanalytic methods are "unwise and may do harm" and also that "direct inquiries into motive and difficulties are better avoided, at any rate in the earlier stages and the youthful cases" Sheldon<sup>13</sup> (1937), on the other hand, who made a careful study of the medical aspects of the disease, reported the successful use of "psychological" treatment

The history of the separate development of medical thought on the twin subjects of Simmonds' disease and of anorexia nervosa is an instance of the difficulties which arise from too specialized an approach,

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47 Stephens, L. *Lancet* 1 31, 1895

whether the emphasis is on the physical or on the mental aspects. It is an illustration also of the extreme complexity of disease in man and the necessity for evaluation of all the factors, if further progress is to be made.

#### SUMMARY

This report concerns 6 patients, 3 of whom were thought at one time to have pituitary cachexia, or Simmonds' disease, and all of whom proved to have anorexia nervosa. Apart from the psychic aspects, the symptoms, physical signs and laboratory findings differed in no essential from those reported in the literature in cases of Simmonds' disease in which the diagnosis was proved at autopsy. In both diseases the manifestations are those of inanition. In the diagnosis of a destructive lesion of the anterior lobe of the pituitary body when there is no evidence of an expanding lesion of the anterior lobe, the chief clues are the age and the number of pregnancies. The use of the therapeutic test, as expressed or implied in the literature, is criticized. It should be postponed until extracts of sufficient potency can be injected safely and until the dose necessary to produce an effect in man has been established. The diagnosis of Simmonds' disease should be withheld until persistent efforts have been made to demonstrate a neurosis and to relieve it if present or until attempts have been made to increase the intake of food and vitamins. Even then the diagnosis may remain in doubt until autopsy.

Simmonds' disease, in the sense of a destructive lesion of the pituitary body, is rare. Whether milder grades occur in patients with anorexia nervosa is speculative at present. Evidences of preexisting ovarian insufficiency are not uncommon.

Replacement therapy in cases of the type of condition often diagnosed as Simmonds' disease rests on an extremely insecure basis. The diagnosis is completely uncertain, and there is no conclusive demonstration of the action of the extract of the anterior lobe, either in proved cases of Simmonds' disease or in pituitary dwarfs who have passed the normal age of puberty.

In the treatment of our patients who had anorexia nervosa, no physiologic effect of the extract of the anterior lobe could be demonstrated. The doses were small. Insulin was used in case 1 and caused a powerful stimulation of the appetite. In case 3 it was received elsewhere without benefit. The administration of thyroid in case 4 was accompanied by an alarming acceleration in the loss of weight. The effect of a vitamin supplement could not be estimated, but the patient who made the most dramatic recovery received none. An adequate intake of vitamins is nevertheless of obvious importance.



The danger of coercive measures designed to increase the intake of food became obvious in cases 3 and 6. Further instances are cited in the literature. Such attempts are directed at the presenting symptom rather than at the cause. The treatment is essentially that of the neurosis. This should not imply neglect of the purely medical aspects of the case.

The differential diagnosis of Simmonds' disease and anorexia nervosa as well as the treatment presents a complex problem. This cannot be met adequately from any limited point of view but must be considered as a whole.

NOTE—With respect to case 2, the patient returned to the outpatient clinic in September 1938 and reported having had six regular menstrual periods beginning on April 17. Her weight was 44 Kg (97 pounds). She continued in a precarious mental state.

With respect to case 5, in retrospect a deficiency of vitamin B must be considered as a cause of the edema.

With respect to case 6, on March 1, 1938, spontaneous menstruation was resumed and continued, with a cycle of twenty-four to forty-three days, October and November being omitted. Her most recent menstrual period was from Dec 20 through 23, 1938.

Miss Margaret Rouchelleau and Miss Bettina Rhett gave nursing and administrative assistance during this study.

# SPONTANEOUS PNEUMOTHORAX ASSOCIATED WITH MASSIVE ATELECTASIS

AN EXPERIMENTAL AND CLINICAL STUDY

LUCILO ESCUDERO, M D

AND

W E ADAMS, M D

CHICAGO

Spontaneous pneumothorax in man is not uncommon. Although formerly thought of as usually associated with tuberculosis of the lungs, it is now known to occur secondary to some congenital anomaly or to nontuberculous infection of the lung in a high percentage of cases.

Spontaneous pneumothorax associated with massive collapse of the lung, either postoperative or secondary to bronchial obstruction, has been infrequently observed<sup>1</sup>. There is as yet no definite evidence to explain the mechanism of this interesting phenomenon. The present report deals with the experimental production of spontaneous pneumothorax in 8 dogs and in 1 goat and with a clinical case of spontaneous pneumothorax associated with atelectasis.

## EXPERIMENTS

Complete atelectasis of the right or of the left lung was produced in animals by the silver nitrate technic<sup>2</sup> during the investigation of several problems dealing with operations on the lungs. This entailed the cauterization, through a bronchoscope, of the entire circumference of the mucous membrane of a primary bronchus with a 35 per cent solution of silver nitrate. Complete stenosis of the bronchus resulted about two weeks after cauterization and was verified by bronchoscopic examination. A diagnosis of massive atelectasis was made by finding dulness to flatness over the side collapsed, with displacement of the

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From the Department of Surgery of the University of Chicago

1 Cummings, R. E. Pneumothorax in Massive Collapse of the Lung in Pneumonia, *Arch. Pediat.* **52**: 623, 1935. Aldridge, C. B. M. Pneumothorax Following Pneumonia, *Brit. M. J.* **2**: 926, 1915. Menetrier, P., and Pascano, A. Pneumonia et pneumothorax, *Bull. et mem. Soc. med. d. hôp. de Paris* **39**: 657, 1914. Jones, B. B. Spontaneous Pyopneumothorax Complicating a Case of Lobar Pneumonia, *Virginia M. Monthly* **51**: 98, 1924.

2 Adams, W. E. Detailed Description of a Safe and Reliable Method for Closing Large Bronchi, *J. Thoracic Surg.* **3**: 198, 1933.

cardiac impulse to that side. Fluoroscopic and roentgenographic study of the chest showed massive atelectasis of the stenosed lung, the heart, the diaphragm and the chest wall were displaced toward the collapsed lung. The remaining lung became distended and showed dilatation of the bronchial tree.

Fluoroscopic and roentgenologic examinations of the chest revealed spontaneous pneumothorax in 8 instances in dogs and in 1 instance in a goat (fig 1). Routine roentgenologic examinations were not usually made after the occlusion of a bronchus, and thus instances of this phenomenon probably went unobserved.

The pneumothorax appeared as soon as three days after the bronchial occlusion. The air was observed on the side of the remaining

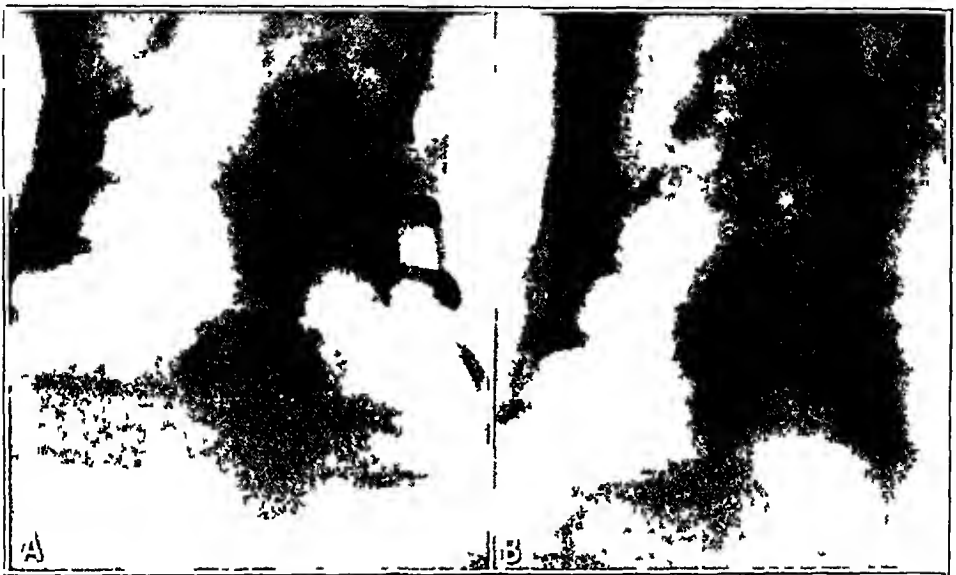


Fig 1—*A*, goat's lungs, showing massive collapse of the left lung, with spontaneous pneumothorax. *B*, lungs of the same goat one month later, showing complete reabsorption of air in the left side of the chest.

inflated lung in only 1 dog. In all others, the air was on the side of the massive collapse. The location of the pneumothorax was variable, sometimes being in the upper portion of the pleural cavity and in other instances being in the lower portion. Its evolution was followed by repeated roentgen examinations, and the reabsorption of the air was observed in from one to two months (figs 2 and 3).

Dog 1—May 13. A septic embolus containing a lead pellet was lodged in the lobe of the left lung by being liberated in the blood stream through the jugular vein.<sup>3</sup>

3 Cutler, E. C., and Schlueter, S. A. Experimental Production of Abscess of the Lung, *Ann Surg* **84** 256, 1926. Holman, E., Weidlein, I. F., and Schlueter, S. A. A Method for the Experimental Production of Lung Abscess, *Proc Soc Exper Biol & Med* **23** 266, 1926.

May 15 A fluoroscopic examination revealed the lead pellet in the lobe. An insignificant lesion developed and healed, and it was decided to use this animal in an attempt to collapse as much of the lung tissue as the endurance of the animal would permit

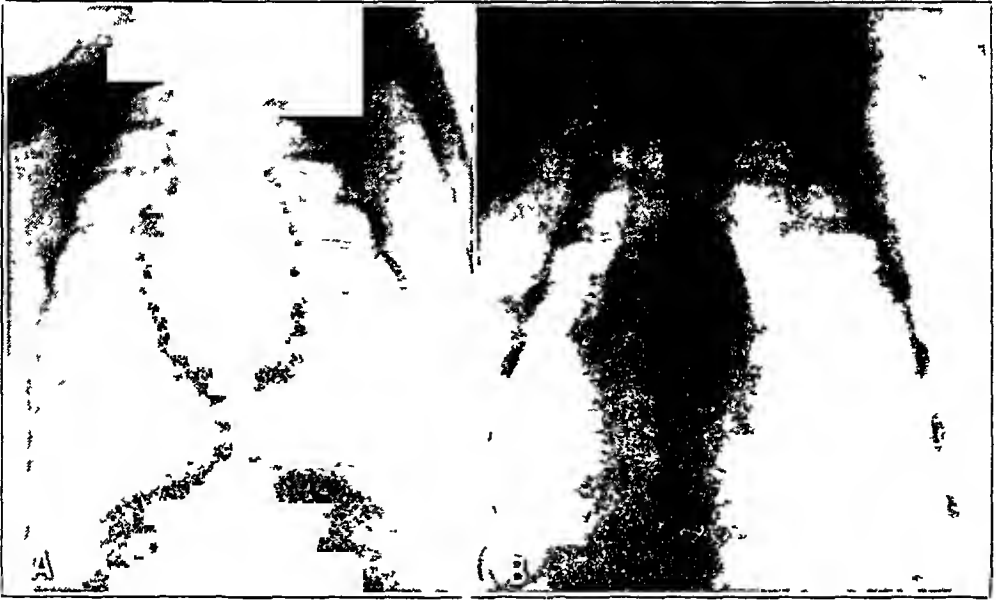


Fig 2—*A*, the chest of dog 1 *B*, the chest of the same dog, showing massive collapse of the right lung and spontaneous pneumothorax on the right side. Note the lead pellet in the lower lobe of the left lung

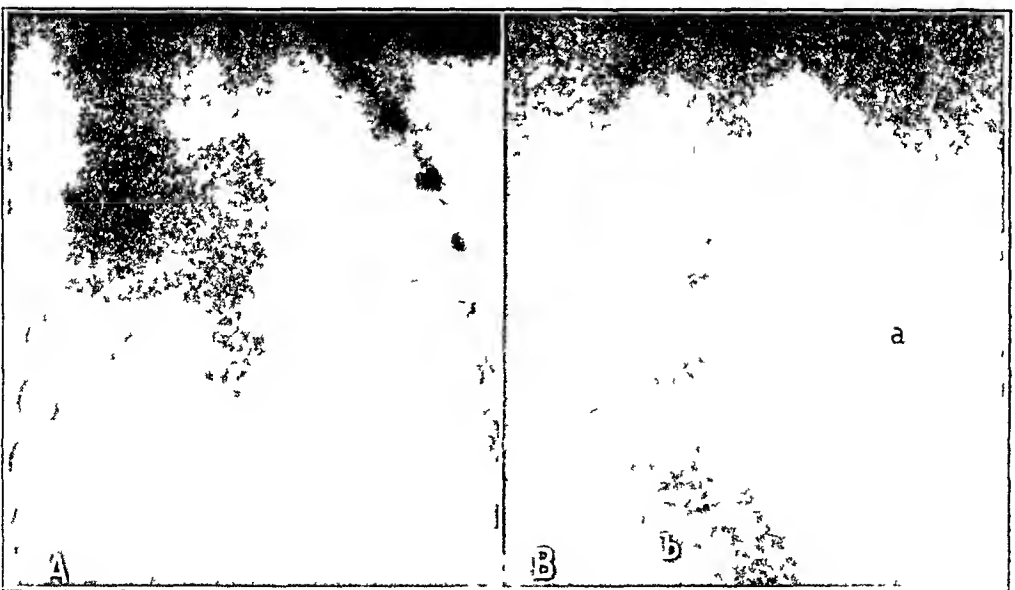


Fig 3—*A*, dog 1, five weeks later. Most of the air in the right pleural cavity has been reabsorbed. *B*, dog 1, twelve days after cauterization of the bronchus of the lower lobe of the left lung. Note the interlobar fissure at *a* and the lead pellet at *b*. The lower lobe of the left lung has not yet collapsed

June 19 The right primary bronchus was cauterized with a 35 per cent solution of silver nitrate. This was applied through a bronchoscope with the animal under morphine anesthesia

July 3 Bronchoscopic examination showed the primary bronchus on the right side to be stenosed to the point that it measured only 3 mm in diameter Silver nitrate solution was reapplied

August 22 A very small opening remained in the bronchus as seen with the bronchoscope The solution was reapplied

September 6 There was no change in the bronchial opening The solution was reapplied

September 22 Bronchoscopic examination showed complete stenosis of the bronchus The right side of the chest was dull on percussion, and the cardiac impulse was plainly felt on the right side

September 25 The dog breathed so rapidly that it was almost dyspneic Fluoroscopic examination revealed massive collapse of the right lung with the heart deviated to the right, but there was also spontaneous pneumothorax on the right side Roentgenograms confirmed the fluoroscopic observations (fig 2 B)

October 6 No change was evident fluoroscopically

October 30 Roentgen examination revealed almost complete disappearance of the pneumothorax (fig 3 A)

April 6 Bronchoscopic examination showed the primary bronchus on the right to be completely occluded The bronchus of the lower lobe of the left lung was cauterized

April 29 The bronchus of the lower lobe of the left lung had closed down to 5 mm in diameter It was recauterized

May 11 At 11 a m the dog was dyspneic and restless Respirations were slow and labored At 2 p m a roentgenogram revealed massive collapse of only the right lung, with the mediastinal structures deviated toward the right (fig 3 B) An electrocardiogram showed no abnormalities At 5 p m there was no change clinically Dyspnea was extreme A roentgenogram revealed massive collapse of the right lung and also of the lower lobe of the left lung, the lead pellet being shifted in position with the collapse of this lobe (fig 4 A) There was a very large spontaneous pneumothorax on the right side—a spontaneous pneumothorax for the second time in this animal A second electrocardiogram revealed little change

May 12 At 8 a m the dog appeared somewhat less dyspneic A roentgenogram and an electrocardiogram showed little change When these examinations were repeated at 2 p m, the same results were obtained

May 13 The dog was less dyspneic The appearance of the chest was little changed (fig 4 B)

During the following twelve days the dog ate well, was up and about and appeared normal, although slightly dyspneic

May 25 The dog was found dead in its cage at 8 a m The animal was frozen before the chest was opened Much of the air in the chest had been reabsorbed There was massive atelectasis of all lobes of the lungs except the upper lobe of the left lung, which was enormously hyperinflated, partially filling the space no longer occupied by the other lobes

The mechanism of production of the spontaneous pneumothorax has been difficult to explain The most plausible explanation is as follows With the production of massive atelectasis, the loss in volume due to the collapse of the lung is compensated for by the hyperinflation which results in the remaining, aerated lung If the pleura of this distended lung is overstretched, it may burst and give rise to the pneumothorax

If, however, the air is liberated into the pleural cavity of the inflated side, an explanation must be forthcoming for its presence on the opposite (collapsed) side. It was found that the intrathoracic pressures in the sides of the chest of a dog with atelectasis were different. From between  $-6$  and  $-8$  cm. of water, which is the normal negative pressure in the dog, it increased to between  $-8$  and  $-10$  in the aerated side and reached a level between  $-14$  and  $-18$  in the atelectatic side. Thus it was thought that the air liberated from the hyperinflated lung was drawn into the side of the massive collapse owing to the higher negative pressure prevailing in this side of the chest.

Of course, if the foregoing explanation is correct, the air liberated into the distended side has to pass through the mediastinum to reach

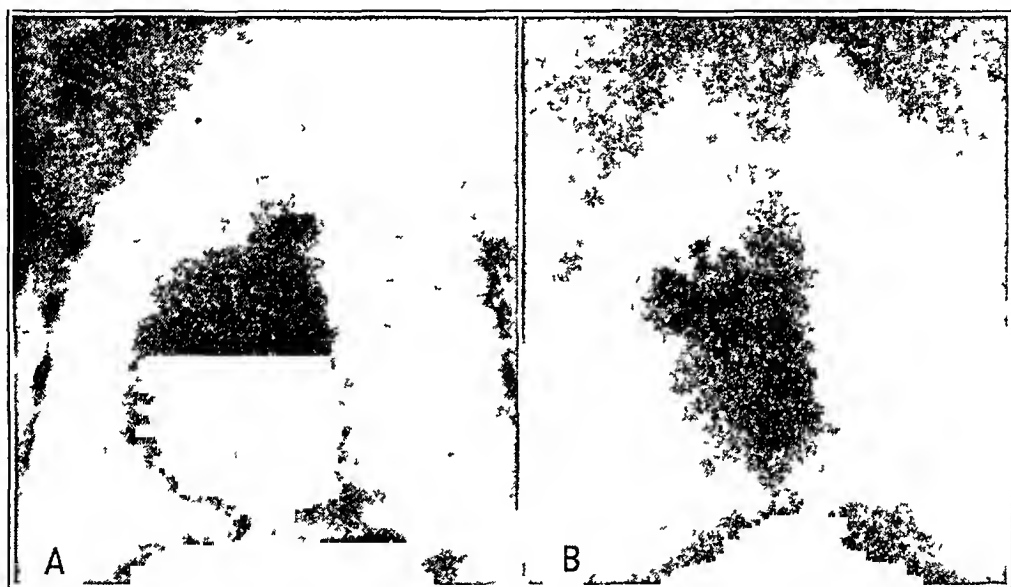


Fig 4—*A*, roentgenogram taken three hours after that shown in figure 3 *B*. The lower lobe of the left lung, as well as the entire right lung, is completely atelectatic. Note the large spontaneous pneumothorax and the shift of the mediastinal structures. *B*, roentgenogram taken two days later, showing little additional change.

the opposite pleural cavity. Although it is well known that the mediastinum in the dog is much thinner than that in man, the following experiment was planned in order to demonstrate the permeability to air of the mediastinal structure in this particular case. After complete atelectasis of the left lung had been produced, air was deliberately introduced into the opposite pleural cavity under fluoroscopic control. The air was seen to leave the injected pleural cavity and to fill up the atelectatic side (fig 6). Thus it was proved that air liberated into the pleural cavity of the inflated side would pass immediately through the mediastinum into the pleural cavity of the atelectatic side and that

the increased negative pleural pressure of the collapsed side probably sucked the air of the opposite side through the mediastinum. The pressure on both sides of the chest then became more nearly equalized, and the mediastinum returned to a position more nearly normal. The experiment was repeated, and the same results were obtained. In cases of spontaneous pneumothorax the air liberated into the pleural cavity would decrease the size of the hyperinflated lung and thus allow the ruptured region to close again. The air would then be slowly reabsorbed.



Fig 5—Roentgenogram of the chest of a dog, showing massive collapse of the right lung, with spontaneous pneumothorax, after complete stenosis of the primary bronchus on the right side

Dog 2—April 1. Bronchoscopic examination was made with the animal under morphine anesthesia. The primary bronchus on the left side was cauterized with a 35 per cent solution of silver nitrate.

April 14. A roentgenogram of the chest revealed massive collapse of the left lung (fig 6A). The pressure in the right pleural cavity was  $-12$  cm. With the aid of morphine anesthesia and fluoroscopic control, 250 cc of air was introduced into the right pleural cavity. The pressure then read  $-6$  cm. Although the air was introduced into the right pleural cavity, on fluoroscopic and roentgenologic examination it was found only on the left side.

May 1 A roentgenogram revealed complete reabsorption of the air during the two week interval since the pneumothorax had been induced

The experiment was repeated, the pressures being found the same as on April 14 A total of 175 cc of air was introduced into the right pleural cavity Again the air was observed only on the left side (the collapsed side) on fluoroscopic and roentgenographic examination (fig 6B)

*Comment*—In dog 1, further atelectasis to the extent of all but one lobe (the upper lobe of the left lung) was produced As the last collapsed lobe was becoming atelectatic spontaneous pneumothorax developed for the second time in this animal The dog lived for fourteen days in spite of the reduction in the functioning of the pulmonary parenchyma and the presence of a large pneumothorax Cases of spon-



Fig 6—A, roentgenogram of dog 2 showing massive collapse of the left lung B, the same dog after 175 cc of air had been introduced into the right pleural space Note that pneumothorax is on the left side only and that the heart is lifted away from the thoracic wall

taneous pneumothorax associated with atelectasis reported in the literature have usually been secondary to a pneumonic process or to massive collapse of the lung Of 7 cases of pneumonia reported by four authors 5 were in adults with three deaths the other 2 were in children with one death and one recovery In general spontaneous pneumothorax complicating pneumonia was thought to present a poor prognosis

L R Sante<sup>4</sup> described a case of massive atelectasis of the lung associated with pneumothorax The condition appeared after an asth-

4 Sante L R Massive (Atelectatic) Collapse of the Lung, with Report of a Case Showing Associated Spontaneous Pneumothorax Am J Roentgenol 20 213, 1928



matic attack. A roentgenogram of the chest showed a small area of the upper lobe of the left lung still aerated, the remainder of the lung being atelectatic. Sante believed that the change in pressure conditions resulting from the development of atelectasis caused a bleb of this aerated portion to burst, permitting an onrush of air into the pleural cavity and the formation of the pneumothorax. F. G. Dorwart<sup>5</sup> reported a case of spontaneous pneumothorax associated with atelectasis which was observed eleven days after heminephrectomy; he agreed with Sante in its interpretation. In both cases, the massive collapse of the lung disappeared after the patient had been rolled over on the unaffected side, the pneumothorax being gradually absorbed and the recovery of the patient being uneventful. Thus the prognosis probably depends largely



Fig 7—Anteroposterior and lateral views of a child 8 months old. Note the spontaneous pneumothorax in the upper part of the right side of the chest, with the atelectatic lung beneath.

on the underlying pathologic process (pneumonia, massive collapse, etc.) rather than on the complicating pneumothorax.

#### REPORT OF A CASE

In reviewing the cases of atelectasis observed at this clinic, we found a case associated with spontaneous pneumothorax. A summary of the history follows:

C. D., a Negro girl 8 months old, had begun to cough noticeably two months before admission. Loss of appetite, increasing irritability and fever followed.

<sup>5</sup> Dorwart, F. G. Postoperative Pneumothorax—Case Report, and Consideration of Factors That Might Be Concerned in Its Etiology, *J. Oklahoma M. A.* 28:205, 1935.

Cough and fever persisted. The child showed undernourishment on admission, and a tuberculin test was positive with a dilution of 1:5,000 on two visits in the outpatient clinic. The temperature was 101° F. The physical examination revealed a large amount of air in the right side of the thorax.

On fluoroscopic examination, the diaphragm appeared somewhat depressed on the right side and showed limited excursion. There was a large pocket of air in the upper half of the right pulmonary field, nearly complete consolidation of the middle third of the right lung, with what appeared to be a second pocket of air in its center, and frankly abnormal densities in the lower half of the right pulmonary field, extending downward from the hilus. With the child held erect on the fluoroscope, the apparent pocket of air seen in the middle third of the lung field in the horizontal position had disappeared. No pocket was seen in the middle third. A rather wide upper mediastinal shadow and definite displacement of the trachea nearly a centimeter to the left of the midline were noted.

Anteroposterior and lateral roentgenograms of the chest revealed a large pneumothorax occupying the upper half of the chest, with an opacity just beneath it resembling a collapsed pulmonary lobe. The left pulmonary field was normal (fig. 7).

The diagnosis was spontaneous pneumothorax associated with massive atelectasis. The patient did not return, and the case could not be followed further.

# CONCLUSION

It is interesting that the spontaneous pneumothorax in atelectasis, so rare in man, has been observed nine times in this experimental work. It seems, to judge by these observations, that the appearance of the phenomenon is more frequent in dogs than in human beings. Probably the extension of the atelectasis, on the one hand, and the differences in the constitution of the lung and of the mediastinum, on the other, account for these variances. In human beings the atelectasis is limited to a part of one lung, the remainder being distended and considered the source of the pneumothorax which is produced in the same side of the chest. In the experimental animals, the atelectasis involved one complete lung, thereby increasing considerably the negative pleural pressures, the source of the air was in the contralateral aerated lung. In cases of complete atelectasis of one side in human beings, as seen in patients with massive collapse of one lung, the thick and more stable mediastinum, together with a visceral pleura fairly thick in comparison with the same structure in dogs, can explain the lack of development of spontaneous pneumothorax. The mobility and permeability of the mediastinum of the dog are sufficient reason both for the fact that the atelectasis of one side exerts a greater influence on the other lung in this animal than it does in man and for the passing of the air from the aerated to the collapsed side of the chest.

## SUMMARY

Spontaneous pneumothorax associated with atelectasis was observed in 9 animals and in 1 human being. Experiments were carried out which proved that simple overdistention of the lung complementary to massive atelectasis, without the presence of external trauma or some other pathologic process in the second lung, is sufficient for the development of spontaneous pneumothorax. This type of mechanism—i. e., increased intrapleural negative pressure with overdistention of the non-collapsed lung—could explain some of the cases of spontaneous pneumothorax associated with atelectasis seen clinically.

# ENDOCRINE MANIFESTATIONS IN JUVENILE DIABETES

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The search for clinical evidence of endocrine imbalance in juvenile diabetes has become imperative because the results of present day physiologic research indicate that experimental diabetes is a disturbance of endocrine regulation. The importance of these investigations rests not only with the fact that from the combined data of the laboratory and the clinic the mechanism of diabetes may be explained and its cause and prevention indicated but also with the possibility that a more nearly perfect form of treatment may be developed.

The physiologist's point of view has been summarized by Houssay<sup>1</sup> in a classic article entitled "Diabetes as a Disturbance of Endocrine Regulation," published in 1937. He has defined diabetes as a disturbance of carbohydrate metabolism in which the normal balance of regulating factors is altered. The muscular disturbances are secondary to functional changes in the liver and in the hormonal output of the pancreas, the pituitary body and the adrenal gland. In this regulation the liver holds the most important part, because it produces dextrose and governs the sugar content of the blood under hormonal influences. The internal secretion of the pancreas maintains the blood sugar at a normal level. It is governed by the level of the blood sugar and vice versa. The secretion of the anterior lobe of the pituitary body normally prevents hypoglycemia and the decrease in glycogen. Excess activity of the anterior lobe increases resistance to insulin and decreases the endogenous production of insulin. The sympatheticoadrenal function is antagonistic to insulin. Lack of activity of the adrenal cortex results in hypoglycemia and amelioration of pancreatic diabetes. Activity of the thyroid gland favors the destruction of glycogen and decreases its formation. The gonadotropic hormones and the pregnant state can influence diabetes possibly through the pituitary body, the liver or the adrenals, and thus a suggestive conception of the diabetic state follows that the pancreas exercises an antidiabetic influence and the anterior lobe of the pituitary, the adrenal and the thyroid gland have a diabeto-genic influence. In all cases of diabetes a relative insufficiency of insulin

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<sup>1</sup> Houssay, B. A. *Am. J. M. Sc.* **193** 581, 1937

exists, although the endogenous production of insulin may be normal or increased. In all cases of diabetes an anterior pituitary factor and perhaps adrenal, thyroid and gonadal factors exist. This point of view of clinical diabetes stresses search for evidence of hyperfunction or hypofunction of the various endocrine glands in the diabetic or the prediabetic state, correlation of findings with those of the physiologic laboratory and a summarizing of the effects of deprivation and substitution therapy in the treatment of the disease.

#### MATERIAL

Because of the well known lack of evidence of a pathologic condition of the pancreas in juvenile diabetes,<sup>2</sup> the young patient lends himself well to this investigation. A review of the data concerning 1,250 patients with juvenile diabetes (onset of the disease before the age of 15 years) indicated that 177 showed evidence of prolonged pituitary involvement. Of these 177 patients, 176 showed involvement related to the anterior lobe of the hypophysis (9 with signs of hyperactivity and 168 with signs of hypoactivity). Among these patients were 94 dwarfs, 22 with Frohlich's syndrome and 51 with signs of infantilism. Only 1 patient had signs and symptoms related to the posterior lobe of the hypophysis. None of the 1,250 patients exhibited signs of deficiency of the thyroid gland, 3 had signs of hyperthyroidism, 1 had possible adrenal disturbance and 28 had lesions related to the gonads. All, presumably, showed hypofunction of the pancreas, but 2 presented signs of hyperinsulinism in addition. Sixty-five had disturbances of the liver which may or may not have been of endocrine origin. Thus, a fourth of all the diabetic children whom my colleagues and I have studied in this clinic appeared to have well marked and persistent evidence of disturbance of endocrine balance.

#### ANTERIOR LOBE OF THE HYPOPHYSIS

Of all the endocrine glands involved in carbohydrate metabolism and, presumably, in diabetes, the most important, exclusive of the pancreas, is the anterior lobe of the hypophysis. Within the past ten years the four following important physiologic observations have been made. First, Houssay<sup>1</sup> reported amelioration of diabetes of depancreatized toads, cats and dogs by hypophysectomy, second, aggravation of diabetes in the Houssay<sup>1</sup> animal was caused by injections of crude anterior pituitary extract, third, prolonged glycosuria was produced by Evans<sup>3</sup> in animals treated with injections of an anterior pituitary extract that

2 Warren, S. Pathology of Diabetes Mellitus, Philadelphia, Lea & Febiger, 1930. White, P. Diabetes in Childhood and Adolescence, *ibid*, 1932.

3 Evans, H. M. Proc Soc Exper Biol & Med **30** 370, 1933.

was rich in the growth factor, and fourth, this work culminated in the experiments of Young,<sup>4</sup> who, with an extract of anterior pituitary substance prepared according to the method of Schockaert, produced permanent diabetes without pancreatectomy.

One naturally asks, What profound changes have these experiments in endocrine deprivation and endocrine therapy produced, how are they brought about and how may they be related to clinical diabetes? It is well known that removal of the anterior lobe of the pituitary<sup>1</sup> results in atrophy of all the endocrine glands except the adrenal medulla. It increases the islet tissue of the pancreas, lowers the basal metabolic rate and produces hypoglycemia, a diminution of glycogen storage and glycogenolysis. The following factors that are augmented by injections of anterior pituitary extract have been described: first, a pancreatropic factor<sup>5</sup> which is beneficial to the diabetic state and, second, a diabetogenic factor which consists of two parts, glycosuric and ketogenic. According to Houssay, the diabetogenic factor acts on the tissues producing resistance to insulin and depresses the endogenous secretion of insulin, it is ineffective in the absence of the liver. A few experiments on human beings with diabetes are believed to have indicated the possible presence of this diabetogenic substance. Thus, the blood of adult diabetic patients is said to render rabbits resistant to insulin and is believed to create glycogenolytic action in rats.

From the clues suggested by physiologic experiments, one must turn to clinical data and, first, search through it for evidence of hypersecretion of the pituitary gland in juvenile diabetes, second, search for the explanation of an apparent physiologic contradiction, namely, the great incidence of hypopituitarism in these patients, and, third, attempt to summarize the work which has been done regarding deprivation and substitution therapy. The search is not in vain, for, first of all, one finds that overgrowth is the most common precursor of juvenile diabetes, 87 per cent of 303 of our children for whom we have the data were overheight prior to the onset of the disease, the average excess height being 2.4 inches (6.4 cm). The average osseous development observed roentgenographically and reported by Bogan and Morrison<sup>6</sup> was eighteen months in advance of the chronologic age, and the dental development was twelve months in advance. The basal metabolic rate in 86 cases was, on the average, plus 12 per cent (essentially normal), and the average intelligence quotient of 169 of our diabetic children was 10 points higher than that of the normal controls.

The age incidence of juvenile diabetes also follows peaks of increasing activity of the pituitary gland. These peaks are believed to occur

<sup>4</sup> Young, F. G. *Lancet* **2** 372, 1937.

<sup>5</sup> Anselmino, K. J., and Hoffman, F. *Ztschr. f. klin. Med.* **129** 24, 1935.

<sup>6</sup> Bogan, I. K., and Morrison, L. M. *Am. J. M. Sc.* **174** 313, 1927.

at 6 and 12 years of age. The role of growth in relation to the production of diabetes and its presumed relation to the anterior lobe of the hypophysis has recently been demonstrated in experimental diabetes. Thus, Long<sup>7</sup> has shown that in the depancreatized infant rat, diabetes does not develop immediately but only coincidentally with growth on the nineteenth day of life. A correlation exists at this point between juvenile and adult diabetes. Obesity is the most common precursor of diabetes in the adult, overgrowth, in the child. The most common age of onset is 53 years, when, in women particularly, anterior pituitary hormones, such as the gonadotropic principle, are produced in excess. Although obesity is commonly associated with hypofunctioning of the pituitary body, there are diseases of hyperactivity, such as pituitary basophilism, in which it is a common finding. But more striking than this evidence was the result of Young's<sup>8</sup> experiment. After repeated injections of an anterior pituitary extract, his dogs became extremely obese prior to the onset of diabetes. In our own work with a similar extract, marked obesity often preceded the growth in stature.

Evidence of hyperactivity does not persist in the course of juvenile diabetes. Thus, after several years' duration we find not only that the average height and weight of our children were essentially normal but 94 children (approximately 8 per cent) were actually dwarfish, to the extent of being 4 to 13 inches (10 to 33 cm) below the standard height for their age.

Dwarfish in diabetes has long been considered a puzzling problem and a physiologic contradiction. The high incidence of dwarfish in our own series, however, we must emphasize, is not representative. Because of our interest in the association of these two conditions, we have sought dwarfish diabetic children whenever and wherever possible. Diabetic dwarfish follows and does not precede the onset of diabetes. Although we do not have the data for the height at onset in all cases, we do have the data obtained within the first year of onset for 36 patients, and these indicate that the subjects were typical tall diabetic children. Dwarfism was not recognized as a rule until the fifth year of diabetes. The shortest duration was four years. There was male predominance, 59 of the 94 children showing dwarfish being boys and 35 being girls.

As early as 1925 a group of these dwarfish children were recognized and because of this early recognition and the time relation to the period of undernutrition therapy, we concluded that their dwarfish was the result of the form of treatment. However, the number of dwarfish children increased in spite of the use of improved diets, and to explain this we concluded that undernutrition resulted from uncon-

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<sup>7</sup> Long. Personal communication to the author.

controlled diabetes. Although we cannot rule out lack of control of diabetes, with time it became evident that uncontrolled diabetes is not inconsistent with normal rates of growth and development.

A study of the physical characteristics of these children shows that they had the type of dwarfism associated with pituitary deficiency or pituitothyroid deficiency. The hair was fine and sleazy, the skin was delicate, often covered with lanugo, dental development was normal though sometimes delayed, osseous development was either normal or delayed, the epiphyses tended to close rather late, at 22 or, more rarely, at the normal time, 18, the intelligence quotient was, on the average, 94, the range being from 60 to 120, and the psyche remained childish. Puberty occurred late, the menarche in 10 girls was established at an average age of 16.5 years, but the onset of catamenia had not occurred in 12 others whose ages varied from 15 to 23, the average age being 18 years. The basal metabolic rate was, on the average, plus 14 per cent. The uric acid content was normal, 2.8 mg. The liver was enlarged in 34 of the patients, so that sometimes a mistaken diagnosis of von Gierke's disease was made. Either the ratio of sitting height to standing height was normal or there was an obvious defect in the lower segment. Reproduction was not inconsistent with dwarfism. Thus, of the former dwarfs, 4 have married, two pregnancies have occurred among the girls in the series, although none among the wives of the former dwarfish boys.

In favor of the diagnosis of pituitary dwarfism, too, in these children is the authoritative opinion of Houssay who, at the time he delivered the Dunham lectures at Harvard, in 1935, gave an opinion about these dwarfs, he said without a moment's hesitation, "They are pure pituitary dwarfs."

There are three possible explanations for the apparent physiologic contradiction. First, the pituitary body in these instances has partially burned out, conceivably it does so in all instances of juvenile diabetes, but in this group of children more quickly than in the average diabetic child. Second, antihormones, including an antigrowth hormone, are produced. A third explanation was suggested by Houssay, that these children have a deficient pituitary gland, which causes a lack of both the growth and the theoretic pancreatic factor. Although each view appears possible, the first seems to be the most logical, namely, that hyperactivity ends in hypoactivity. This observation is not without parallel in other conditions related not only to the pituitary gland but also to other endocrine glands. The acromegalic patient finally dies not of hyperpituitarism but of hypopituitarism. Prolonged administration of the gonad-stimulating factor causes atrophy of the gonads. Prolonged administration of thyroid causes atrophy of the thyroid gland.



and prolonged administration of insulin inhibits secretion of insulin, even when the islet tissue is hypertrophied

If pituitary deficiency has occurred in this group, it should be possible to predict certain characteristic changes (1) that the diabetes during the course of dwarfism would be mild, (2) that the incidence of diabetic coma would be different from that in the series at large, for it could be either low because of the lack of ketogenic hormone or increased because of the diminution in glycogen storage (the incidence was high—45 had had one or more attacks), (3) that the incidence of severe hypoglycemia would certainly be great, and (4) that the incidence of cataracts and arteriosclerosis should be frequent. Actually, we have found that during the course of untreated dwarfism diabetes was mild. The incidence of severe hypoglycemia was great. One child had convulsions almost daily for a year, 3 children were considered to have true epilepsy and a total of 40 had episodes of unconsciousness and convulsions. Four children had cataracts and 13 arteriosclerosis.

Pathologic changes comparable with those found in hypophysectomized animals cannot be reported on because, although the mortality rate for this group was relatively high (12 deaths [13 per cent]), the majority of these children died outside of hospitals. Houssay<sup>8</sup> reported a similar case, in which scars were seen on the pituitary gland. There have been 3 autopsies in our own series, and the observations have not been remarkable.

The result of the treatment of dwarfism in diabetes is of interest not only as an important observation on this form of therapy but also because of the possible result of injections of anterior pituitary extract on the course of diabetes. During the past ten years we have employed the following forms of therapy: diet alone, a high caloric and high protein diet with the addition of thyroid and anterior pituitary preparations administered by mouth (10 patients), and a high caloric diet plus an anterior pituitary extract containing the growth hormone or a high caloric diet plus anterior pituitary extract containing the growth hormone plus thyroid (33 patients). In the group treated by diet alone, 12 females aged 16 years or more finally attained an average stature of 58.8 inches (148 cm), and 17 males aged 18 years or over, an average stature of 63 inches (160 cm). The maximum was 66.5 inches (168 cm). The end results of thyroid treatment were slightly better. The males, on the average, attained a stature of 64.1 inches (162.5 cm). The maximum was 66.8 inches (169 cm). Since anterior pituitary extract has been used more for younger patients, a comparison in corresponding age groups cannot be made at present, but it can be stated that in many instances treatment with this extract tripled the rate of

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<sup>8</sup> Houssay, B. A. Personal communication to the author.

growth Thus, if the child had been growing at the rate of 0.5 inch (1.3 cm) a year, he grew 1.5 inches (3.8 cm), if he had been growing at the rate of 1 inch (2.5 cm) a year, he grew at the rate of 3 inches (7.6 cm) a year. Our most remarkable results have been obtained in an extremely dwarfish girl, who in five months grew 3 inches (7.6 cm), and in a boy, who in ten months grew 5 inches (12.7 cm). The expected normal average and the actual gains of children so treated were 1.5, 1.5 and 2.7 inches (3.8, 3.8 and 7 cm), respectively, for males, and 1, 1.1 and 2.1 inches (2.5, 2.8 and 5.3 cm), respectively, for females.

Treatment of diabetic dwarfism with anterior pituitary extracts containing the growth hormone provides an interesting experiment on the use of anterior pituitary substance, for the substances used are not pure. One of the commercial preparations we employed was designedly complex, containing the gonadotropic, presumably the thyrotropic and possibly the pancreatic factor. The gonadotropic factor was evidenced in our patients, we believed, for those treated with this preparation made a rapid gain in development. As these children were underdeveloped, this was a desirable effect. Theoretically, these preparations may also contain the diabetogenic factor. As a result of administration of these preparations, within two months of the time that treatment was inaugurated there was little change in nitrogen retention. Thus, the increase was from 53 to 57 per cent of the total intake. The average blood sugar values before and two months after the administration of the anterior pituitary extract were essentially the same. This was studied by means of dextrose tolerance tests (18 Gm. per kilogram of body weight). Blood sugar values were taken as in standard tolerance tests (during fasting and at one-half hour, one hour and two hour intervals). Although the average blood sugar values of all patients were the same, the manufacturer whose anterior pituitary extract was designedly crude had reported to us that there was an improvement in carbohydrate tolerance in dogs, and this was demonstrated temporarily in the children. The blood sugar values before and after two months of therapy are shown in the accompanying table. There was no effect on acidosis. One might have expected an increase in incidence because of the ketogenic substance. But the average carbon dioxide-combining power of the blood of 9 patients before treatment was 49 volumes per cent and two months after treatment 53 volumes per cent. After prolonged administration of anterior pituitary extract, diabetes appeared to be somewhat more severe, as measured by the requirement of insulin. Statements concerning the relative severity are open to question because all our children required, with protamine insulin, a larger dose than formerly, but dwarfs treated by means of diet alone required 45 units daily, the average diabetic child, 55, and dwarfs

treated with the anterior pituitary extract, 65 Because the failure of growth is an economic problem, we are willing to sacrifice diabetes for the treatment of this condition

Hormones stimulate the production of antihormones, and thus we sought for evidence either of a permanent beneficial effect on diabetes (which we did not see) or of a harmful effect on growth (this we have not observed)

In addition to the diabetic dwarfs, there was evidence of hypopituitarism in two other groups of patients The first group had infantilism without failure of stature, this was observed in 51 of the children This was not secondary to gonadal insufficiency, because epiphyseal closure was not delayed These children did not become excessively tall and were not of eunuchoid build Compared with the dwarfish children, the sex distribution was nearly even, 27 girls and 24 boys A third class consists of 22 adolescent girls with obesity

*Blood Sugar Values in Grams Before and Two Months After  
Start of Therapy \**

	Preparation A			
	Fasting	One Half Hour	One Hour	Two Hours
Before treatment	0 23	0 35	0 45	0 40
After treatment	0 23	0 36	0 44	0 45
	Preparation B			
	Fasting	One Half Hour	One Hour	Two Hours
Before treatment	0 34	0 41	0 48	0 52
After treatment	0 18	0 30	0 36	0 40

\* A pituitary extract containing the growth hormone preparation was supplied to us for two and a half years by L. R. Squibb & Sons and for seven months by Parke, Davis & Co

resembling that associated with Frohlich's syndrome Other evidence of lack of activity of the pituitary body is found in adult patients, namely, in the frequent occurrence of sterility and the failure of lactation

Evidence of persistent hyperactivity of the pituitary was noted in 9 children The evidence of hyperactivity in the small groups was the excess of stature, a palpable thyroid gland, deep cupping of the optic disks and elevation of the basal metabolic rate

One other possible effect of hyperactivity of the pituitary body may result in still another complication, namely, hepatomegaly Significant enlargement of the liver was noted in 65 children Thus it is known that injections of anterior pituitary extract result in storage of fat in the liver, there is also believed to be a hormone which controls glycogen metabolism and is effective in von Gierke's disease However, adequate data concerning the nature of the enlargement of the liver are at present lacking, and we classify this complication as an end result of uncontrolled diabetes

From the clinical data we have concluded that hyperactivity of the pituitary body precedes the onset of diabetes. It is then followed by hypoactivity in the average case. This is shown by the fact that diabetic children do not continue to gain and maintain a height above the standard rate and also because the course of diabetes is one of mildness, then severity, then stabilization and finally mildness. In its extreme manifestation, this failure of the anterior lobe of the pituitary body results in the diabetic dwarf.

The depression of the activity of the pituitary body by roentgen or surgical treatment is not logical because neither form of treatment is selective. Administration of pituitary substances is believed to produce antihormones. This is a theoretic therapeutic possibility which is being pursued in various physiologic laboratories throughout the world.

#### POSTERIOR LOBE OF THE HYPOPHYSIS

Deficiency of the posterior lobe of the hypophysis has been recognized but once, in an atypical case of temporary diabetes insipidus. During this episode the course of the diabetes was mild. Posterior pituitary extract is useful in the treatment of the disease, however, for of all the contrainsulin substances, we rely more on pitressin than on any other for the treatment of severe insulin reactions complicated by unconsciousness and convulsions.

#### ADRENAL GLAND

The endocrine gland which is of third rank in connection with carbohydrate metabolism is the adrenal gland. Whereas physiologic and clinical observations suggest a possible role in the etiology of diabetes, the reverse relation is not so well defined. Thus, among diabetic patients it is exceptional to find recognizable evidence of adrenal disturbance compared with the number of instances in which signs of disturbance of the anterior lobe of the hypophysis are present. After the discovery of the secretion of the medulla by Blum, in 1901, epinephrine was blamed for the production of diabetes. Although epinephrine is capable of producing hyperglycemia and glycosuria, prolonged administration has not produced diabetes and, presumably the hyperglycemic result is brought about by an increased mobilization of glycogen.

Because Long<sup>9</sup> and Lukens have demonstrated that depression of the adrenal cortex attenuates diabetes in cats and dogs maintained by extract of the adrenal cortex, attention is called to the possible diabetogenic hormone in the adrenal gland. The data are conflicting, however. In

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<sup>9</sup> Long, C. N. H., and White, A. Intermediary Carbohydrate Metabolism, *Ergebn d. Physiol.* **40** 179, 1938.

the laboratory of Long and Lukens, anterior pituitary substance did not aggravate the diabetes of the adrenalectomized animal, whereas in Houssay's laboratory it did. Long suggested three possibilities (1) the pituitary body works through the adrenal gland, (2) the adrenal gland works through the pituitary body or (3) the adrenal gland secretes a diabetogenic substance. As yet injections of adrenal substance have not produced diabetes, whereas anterior pituitary extract produces diabetes without pancreatectomy.

Addison's disease resembles pituitary insufficiency in its effect on diabetes. As one would suppose, it has not been observed in any case of juvenile diabetes. Hyperactivity of the cortex has been associated with the diabetic state in adults. Clinical evidence of hyperactivity in children, however, we have not seen. Thus, none of our girls has shown precocious development, and in the boys there has been no evidence of precocious growth, with production of the so-called Hercules type of child.

There has been only 1 possible case of adrenal disease, a very complicated one. We believe that this 10 year old child, whose diabetes started when she was 1 year old, was a typical pituitothyroid dwarf. In addition to failure of growth in stature, she had a calcified adrenal gland, atrophy of the optic nerves and deep retinal hemorrhages and exudation. During five months of treatment with anterior pituitary extract, thyroid and yeast, in an interval complicated by traumatic fracture of both bones of the lower part of one leg, a peculiar bony overgrowth and destruction of the knee joint, density of all the bones in relation to the epiphyses and a similar destructive lesion in the os calcis developed.

So far as therapeutic suppression of the activity of the adrenal gland is concerned, it is probably illogical. Thus, Rogoff<sup>10</sup> has shown that secretion of the adrenal gland is suppressed and may even be lacking altogether during the course of experimental diabetes.

#### THYROID GLAND

The incidence of thyroid disease in juvenile diabetes in our series, we believe, is somewhat accidental and perhaps the result of the fact that Boston is in a "toxic goiter belt." Thus, among the 1,250 juvenile patients we have seen 3 with typical primary hyperthyroidism. There was nothing remarkable about these patients, they had relatively severe diabetes, and the severity was increased by hyperthyroidism and somewhat decreased but not cured by surgical treatment. No instance of diabetes associated with myxedema or cretinism has occurred in our own

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<sup>10</sup> Rogoff, J. M. *Glandular Physiology and Therapy*, Chicago, American Medical Association, 1935, p. 278.

series of young patients We have a certain number of dwarfish children in whom the growth of the lower segment of the body is defective and who, because of the delayed development of the bones, may be classified as having thyroid or, what we think is better, pituitothyroid deficiency Possibly some of the girls classified as showing obesity of the type seen in the Frohlich syndrome have thyroid deficiency, but this obesity too we have thought to be related to lack of thyrotropic hormone In the literature there are reports of 3 cases of myxedema associated with diabetes in juvenile patients,<sup>11</sup> and recently the remarkable case of an infant who showed signs of cretinism at 3 months was reported to us by Snyder<sup>12</sup> After thyroid feedings, severe diabetes developed, but the diabetes was not relieved by reduction in thyroid therapy and the return of symptoms and signs of cretinism

In the physiologic laboratory, thyroidectomy increases sensitivity to insulin, and thyroid feeding increases resistance to it Theoretically, the action is indirect Hyperglycemia and glycosuria associated with hyperactivity of the thyroid gland result because the metabolism is probably diverted to protein and fat channels and because there are excessive excretion of epinephrine and increased glycogenolysis Thyroid feedings have never induced diabetes

So far as therapy is concerned, thyroidectomy is harmful, for most persons would agree that in the juvenile patient myxedema or cretinism would be infinitely more harmful than diabetes

#### GONADS

The role of the gonads in diabetes in the young is of interest largely in one of three ways first, the possible etiologic relation because of the great incidence of onset of juvenile diabetes at the age of maturity, second, the effects of catamenia on the course of diabetes, and, third, the effect of diabetes on the fatal accidents to the fetus of the diabetic mother

The influence of the gonads as an etiologic factor in diabetes is not shown by the physiologist Thus, removal of the gonads does not prevent the onset of diabetes in the depancreatized animal An increase in sensitivity to insulin is reported, followed by a slight increase in resistance to insulin Although we have attributed some instances of diabetic coma to the onset of the menarche and to the recurrence of catamenial periods, and although some adult patients, whose word we feel is reliable, have reported an increase or decrease in sensitivity to insulin at alternate catamenial periods, the menstrual cycles of 9 girls studied among the

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11 Greenwald, H M, and Collens, W S Hypothyroidism Complicated by Diabetes Mellitus, *Am J Dis Child* 50 979 (Oct) 1935 - - -

12 Snyder Personal communication to the author

110 patients at our girls' summer camp were unconvincing. There was nothing to indicate from their records that there was either increase or decrease in sensitivity to insulin. Perhaps these patients were not typical. Perhaps the accidents of diabetes which occur at this time may be related not to physiologic but to psychic and emotional disturbances. The data should be reexamined.

The accidents to the infant of the diabetic mother, we believe, are largely endocrine. End results have been strikingly poor, even in the insulin era, for only 60 per cent of pregnancies of diabetic women terminate successfully. The characteristic failures are three: miscarriage, stillbirth and neonatal death occurring within twenty-four hours of birth. The great frequency of early miscarriage is now attributed largely to thwarted toxemia predicted by a disturbed balance between gonadotropic substance and estrogen. For years the obstetric diabetic literature has contained accounts of the frequency with which stillborn infants, often described as overdeveloped, have been born to diabetic mothers. Although the effect of diabetes per se cannot be ruled out, we believe that among our own patients the data indicative of this relation have been lacking, for repeatedly it has been our experience that although the mother's diabetes has been under excellent control the infant has died two to eight weeks prior to term. Such accidents are now related to toxemia, a toxemia which is mild so far as the mother is concerned and is predicted by an abnormal relation between gonadotropic substances and estrogen.<sup>13</sup> Here one is reminded of the experiments of Snyder and Hoopes, who showed that injections of the gonadotropic principle from the urine of pregnant women produces a picture not unlike that seen in the pregnancy of the diabetic woman, namely, overdevelopment, death and maceration of a giant fetus. In these experiments the period of gestation was prolonged. In diabetes this is not true. The process of development appears to be speeded up, but there is a tendency to premature rather than postmature delivery. Why this mild toxemia should result in death to the fetus is not understood. Riddle<sup>14</sup> has suggested the possibility that estrogen is the important factor, that it controls the growth and development of the placenta and uterus and that lack of this factor has a profound effect on the welfare of the infant.

The first day of life is hazardous for the infant of a diabetic mother, who differs from the infant of a normal mother in three respects. First, he is a normal person exposed to an intravenous injection of dextrose, second, he is a normal person exposed to the injection of insulin, for circulation of insulin both ways through the placenta has been demon-

13 Smith, G. V., and Smith, O. W. *Am J Obst & Gynec* **33** 365, 1937.

14 Riddle, O. Personal communication to the author.

strated, and, third, he is a normal person exposed to acidosis which may be secondary to diabetes or toxemia. The possible end results are somewhat conflicting. Hyperglycemia may stimulate pancreatic endocrine function, on the other hand, it may exhaust the pancreas. Prolonged administration of insulin may inhibit the secretion of insulin, even though it gives rise to an increase in the number and in the volume of the islet cells.

The blood sugar values and the carbon dioxide-combining power of our last 32 consecutive diabetic mothers and their offspring have been studied carefully. These infants have been grouped as follows: (1) normal infants, (2) abnormal infants who survived and (3) abnormal infants who died. It was found that a low alkali reserve was characteristic in the fatal cases, being, on the average, 30 volumes per cent, compared with 40 for the normal infants and 42 for the abnormal infants who survived. The blood sugar values for the infants of diabetic mothers were, on the average, slightly higher than those of normal controls. It is true that there is a tendency for the sugar content to drop within four hours after birth, but this also occurs in normal infants. The drop is slightly more rapid but not to a lower level than that observed in normal infants.<sup>15</sup> McKittick,<sup>16</sup> studying a group of infants of normal mothers at the Boston Lying-In Hospital, found that a blood sugar value of 25 mg. occurred without clinical signs of abnormality. In our own series of infants the blood sugar value dropped to 9 mg. in 1 instance, 30 mg. in 1, to 40 mg. 3 times and to 50 mg. 7 times. Autopsies were performed in 10 of our fatal cases. Two of the infants were macerated, and therefore autopsy was unsatisfactory. The pancreas was normal in 5 cases and the islet cells were hyperplastic in 3. When this is compared with our blood sugar findings, however, it is found that hyperplasia occurred with normal and with elevated blood sugar values as well as with hypoglycemia, and vice versa.

The chief fatal accident in the neonatal series in our experience has not resembled the hypoglycemia seen in patients treated with insulin or in those few patients with spontaneous hypoglycemia who have been observed but resembles typical asphyxia neonatorum. The asphyxial seizures have not been directly related to the level of the blood sugar, although there was a possible remote relation. Perhaps when the blood sugar level falls it affects the hypothalamus, which is stimulated to produce epinephrine, which in turn may cause the apnea so often fatal to the infant of the diabetic mother. So far as therapy is concerned, perhaps dextrose is good, but since we have been studying the blood

15 Hartmann, A., and Senn, M. J. Alkali Therapy, *Am J Dis Child* **42**, 693 (Sept.) 1931.

16 McKittick, J. B. Personal communication to the author.



sugar curves of the infants, we have postponed it unless the blood sugar level dropped very low and have directed our attention to the treatment of asphyxia, by means of an oxygen-helium incubator

So far as gonadotropic substance in the therapy of diabetes is concerned, it may be of value, because it is known that the administration of an estrogenic substance to depancreatized dogs has resulted in the control of hyperglycemia and glycosuria and longer survival. A beneficial effect has been reported, too, when estrogenic substance has been administered to diabetic patients. It has not been employed in our own series, but we have had an opportunity to study the effect of the ratio of estrogen to gonadotropic substance in the course of diabetes during pregnancy, and our results show that an increase in estrogen was not associated with a favorable change in the diabetic state

#### PANCREAS

The undoubted relation between the internal secretion of the pancreas and diabetes needs little comment here. The experiments of von Mering and Minkowski, who accidentally produced diabetes by pancreatectomy, and the success of therapy with insulin have proved beyond doubt that insulin insufficiency results in diabetes. A few physiologic and pathologic observations are important here as regards therapy for a better understanding of the interrelation of the glands of internal secretion. First, it is well known that the pancreas may be histologically normal, as it is in many instances of severe juvenile diabetes and, second, that insulin is found in the body of the patient with severe diabetes at death. These two facts point to the possibility that overproduction of a diabetic factor results in diabetes and that the suppression of this would alter the course of the disease.

Two of our 1,250 juvenile patients showed evidence of hyperinsulinism along with diabetes. One patient with a mild borderline condition deserves little comment, she never required insulin. The second patient was a girl whose diabetes had existed for ten years and whose requirement of insulin in a few months dropped from 67 to 4 units. At the time of what we believe was an attempted menstrual period, diabetic acidosis developed. The Aschheim-Zondek test gave a positive reaction. She was not pregnant. For a week she required 100 units of insulin a day and then returned to a state of mild diabetes. During the past year she has been treated entirely without insulin. Although diabetes is present for approximately one of each twenty-four hours, unless she has frequent small feedings of carbohydrate, spontaneous hypoglycemia associated with unconsciousness and convulsions develops. The exact cause of this we have not been able to determine because of lack of permission for exploration. The patient prefers hyperinsulinism to diabetes and therefore refuses surgical treatment.

There are three possible explanations of this case. First, the enlarged liver may be the cause of the improvement of the diabetes, second, she may have an adenoma of the islands of Langerhans, and, third, in adult life pituitary insufficiency has developed which is even more marked than that shown by our group of patients with diabetic dwarfism.

#### CONCLUSION

In conclusion, the juvenile patient, even in retrospect, shows evidence of a disturbed hormonal balance. There is striking evidence of hyperactivity of the pituitary body in the prediabetic stage, followed by diminution of activity which in its most extreme form occurs in the diabetic dwarf. Some forms of endocrine disturbance are presumably accidental, namely, those related to the thyroid gland. Although the evidence does not exclude primary insulin insufficiency and although no form of therapy in diabetes yet compares with insulin therapy, this interrelation of the endocrine glands gives the clue for future research. At present investigators throughout the world are searching either for an antihormone other than insulin or for the pancræotropic factor.

# INFLUENCE OF LIQUID PETROLATUM ON THE BLOOD CONTENT OF CAROTENE IN HUMAN BEINGS

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In 1927, Burrows and Farr,<sup>1</sup> and shortly thereafter Dutcher, Ely and Honeywell,<sup>2</sup> working independently, showed that rats were unable to utilize the vitamin A of butter fat when the latter was mixed with liquid petrolatum. Moness and Christiansen<sup>3</sup> later described experiments showing that the utilization of vitamin A from cod liver oil was not appreciably affected by its mixture with liquid petrolatum. Rowntree<sup>4</sup> stated the belief that if the vitamin A of the diet was not "adequate" the addition of liquid petrolatum to the diet of rats would cause a vitamin A deficiency to appear. She compared the effect of liquid petrolatum mixed with small amounts of butter fat with that of liquid petrolatum mixed with small amounts of cod liver oil. Her results interpreted in the light of previous observations by Moness and Christiansen, are essentially like theirs—that the vitamin A of cod liver oil is not affected by the mixing with liquid petrolatum, whereas the

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1 Burrows, M T, and Farr, W K. The Action of Mineral Oil Per Os on the Organism, *Proc Soc Exper Biol & Med* **24** 719-723 (April) 1927

2 Dutcher, R A, Ely, J O, and Honeywell, H E. Vitamin Studies XV. Assimilation of Vitamin A and D in the Presence of Mineral Oil, *Proc Soc Exper Biol & Med* **24** 953-955 (June) 1927

3 Moness, E, and Christiansen, W G. The Assimilation of Vitamin A When Dissolved in Liquid Petrolatum, *J Am Pharm A* **18** 997-998 (Oct) 1929

4 Rowntree, J I. The Effect of the Use of Mineral Oil upon the Absorption of Vitamin A, *J Nutrition* **3** 345-351 (Jan) 1931

vitamin A of butter fat is absorbed by and excreted with liquid petrolatum that is added Jackson<sup>5</sup> repeated the experiments of Dutcher, Ely and Honeywell and noted vitamin A deficiency when the butter fat and the liquid petrolatum were mixed but little diversion of the vitamin A when they were given separately The reason for this distinction was not apparent until Moore<sup>6</sup> showed that carotene and vitamin A were separate substances

Soon after Moore made his announcement, Dutcher, Harris, Hartzler and Guerrant<sup>7</sup> reported experiments showing that crystalline carotene could not be utilized when ingested with a relatively small amount of liquid petrolatum, but that if a carotene-free concentrate of cod liver oil containing vitamin A was fed in conjunction with liquid petrolatum the vitamin A was absorbed from the gastrointestinal tract quite readily These authors further reported experiments showing that when liquid petrolatum was given the excretion of carotene in the feces was proportional to the amount of carotene fed When carotene was fed and liquid petrolatum omitted, the excretion of carotene in the stools was small in amount and remained approximately constant even though the amount of carotene in the diet was increased Mitchell,<sup>8</sup> in 1933, and Jackson,<sup>9</sup> in 1934, feeding foods high in carotene and low in vitamin A, obtained results similar to those of Dutcher and his associates

#### METHOD OF EXPERIMENTS

Previously the experiments have been performed on animals Our observations deal with the effect in man of various amounts of ingested liquid petrolatum on the absorption of carotene from the gastrointestinal tract, as measured by determinations of blood carotene In general, two types of experiments were carried out One consisted in feeding diets lower than normal in their carotene

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5 Jackson, R W The Effect of Mineral Oil Administration upon the Nutritional Economy of Fat-Soluble Vitamins I Studies with the Vitamin A of Butter Fat, *J Nutrition* **4** 171-184 (July) 1931

6 Moore, T Vitamin A and Carotene I The Association of Vitamin A Activity with Carotene in the Carrot Root, *Biochem J* **23** 803-811, 1929, II The Vitamin Activity of Red Palm Oil Carotene, *ibid* **23** 1267-1269, 1929

7 Dutcher, R A, Harris, P L, Hartzler, E R, and Guerrant, N B Vitamin Studies Assimilation of Carotene and Vitamin A in the Presence of Mineral Oil, *J Nutrition* **8** 269-283 (Sept) 1934

8 Mitchell, H S The Influence of Mineral Oil on the Assimilation of Vitamin A from Spinach, *Proc Soc Exper Biol & Med* **31** 231-233 (Nov) 1933

9 Jackson, R W The Effect of Mineral Oil Administration upon the Nutritional Economy of Fat-Soluble Vitamins II Studies with the Vitamin A Factor of Yellow Corn, *J Nutrition* **7** 607-616 (June) 1934

content<sup>10</sup> (2,958 U S P units of vitamin A) in addition to oral feedings three times daily of 45 mg of carotene dissolved in 1 cc of cottonseed oil. The diet and the carotene were fed alone during one part of each experiment and mixed with 20 cc of liquid petrolatum during the other part. The second type of experiment consisted in feeding diets high in carotene, ranging from 24,089 to 32,200 U S P units of vitamin A, and alternating periods when the diet alone was given with periods when various amounts of liquid petrolatum were given. No special attempt was made to mix the liquid petrolatum with the food, but in all experiments except those in which 30 cc of liquid petrolatum was used, the petrolatum was given from one half to one hour before meals. The patients were strictly confined to bed during the experiments. All diets were weighed and consisted of two menus alternated daily to afford variety. Determinations of blood carotene were frequently made on fasting blood by the White and Gordon<sup>11</sup> modification of Palmer's<sup>12</sup> method. All values for blood carotene are expressed in dichromate units<sup>13</sup>.

### RESULTS

Three experiments were conducted with low carotene diets and a mixture of 20 cc of liquid petrolatum and 1 cc of carotene in vegetable oil<sup>14</sup>. This mixture was taken three times daily. Chart 1 shows that during periods of ten and eleven days when the mixture was taken, the blood carotene fell. When the same diet was continued with three additions daily of carotene dissolved in vegetable oil but with the omission of the liquid petrolatum, a rapid rise in the blood carotene occurred.

The objection to this type of experiment may be that the patient was depleted of vitamin A stores before the carotene feeding was begun, and that the failure of the blood carotene to rise during a period was due to a conversion of carotene to vitamin A and its storage in the liver. To answer this objection, we repeated the experiment in reverse order, first feeding the patient a low carotene diet with supplements of carotene dissolved in vegetable oil in amounts of 1 cc three times daily and later adding the liquid petrolatum to the carotene in vegetable

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10 Vitamin A values for foods were computed from average values in the tables of H. C. Sherman (Chemistry of Food and Nutrition, New York, The Macmillan Company, 1937).

11 White, F. D., and Gordon, E. M. The Estimation of the Serum Carotin, *J. Lab. & Clin. Med.* **17** 53-59 (Oct.) 1931.

12 Palmer, L. S. Carotinoids and Related Pigments, New York, The Chemical Catalog Company, 1922.

13 A certain percentage of the yellow pigments which appear in the purified petroleum benzene extract are related to the carotenes but are not vitamin A precursors. As we are dealing with relative changes in the pigments, this error should remain constant. White and Gordon<sup>11</sup> state that each dichromate unit is equivalent to 0.04 mg of carotene in 100 cc of solvent.

14 Each cubic centimeter of the carotene in vegetable oil contained 45 mg of crystalline carotene dissolved in 1 cc of cottonseed oil and contained no less than 7,500 U S P units of vitamin A.

oil Chart 2 shows that a rapid rise of blood carotene occurred when the patient was taking the diet and carotene in vegetable oil When the latter was mixed with liquid petrolatum, a rapid fall of the blood carotene occurred

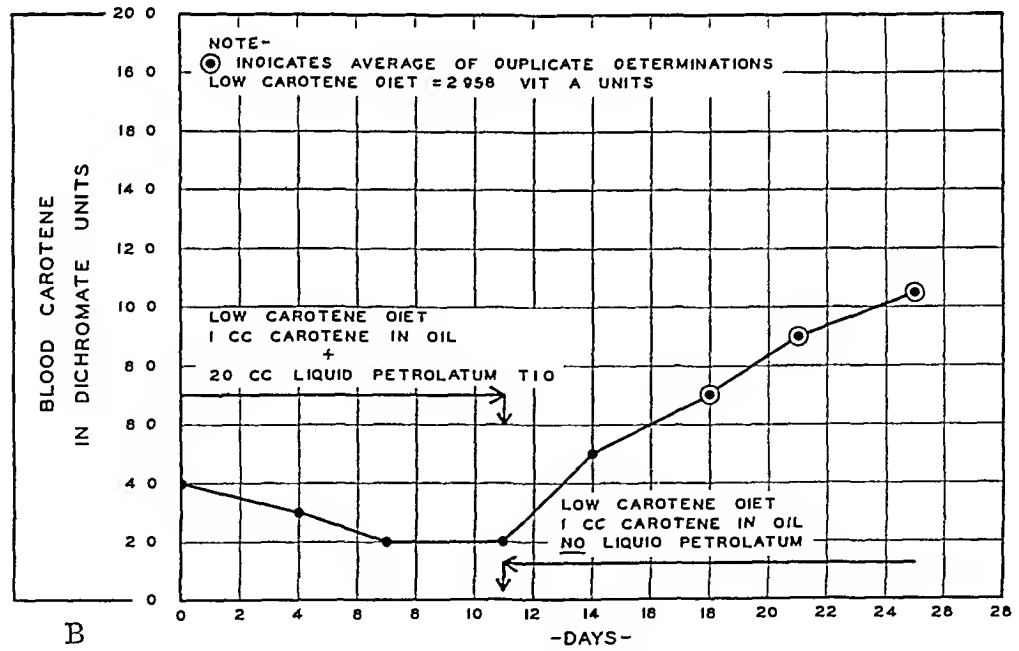
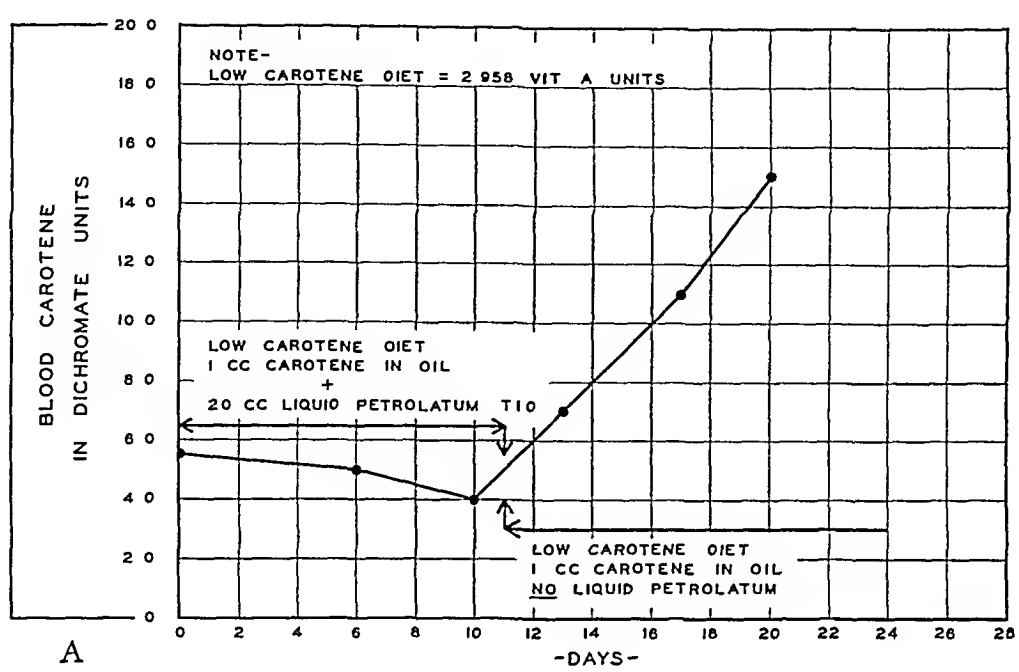


Chart 1—Curves showing the fall in blood carotene that occurred during a period of ten and of eleven days respectively when a mixture of 45 mg of crystalline carotene in 1 cc of vegetable oil was dissolved in liquid petrolatum and given in amounts of 20 cc three times daily before meals to patients on a low carotene diet and the subsequent rapid rise in blood carotene when the same diet was continued with three additions daily of carotene dissolved in vegetable oil, but with the liquid petrolatum omitted

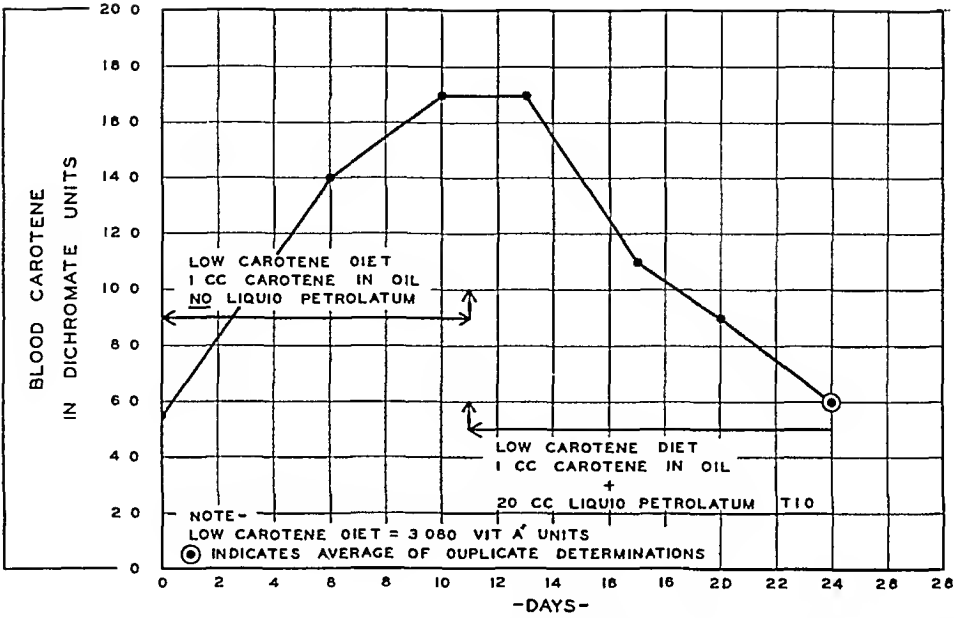


Chart 2—Increase in blood carotene when supplements of 45 mg of carotene dissolved in 1 cc of vegetable oil were given three times daily to a patient on a low carotene diet, followed by a rapid fall when the carotene and vegetable oil were mixed with liquid petrolatum and the mixture given in amounts of 20 cc three times daily before meals

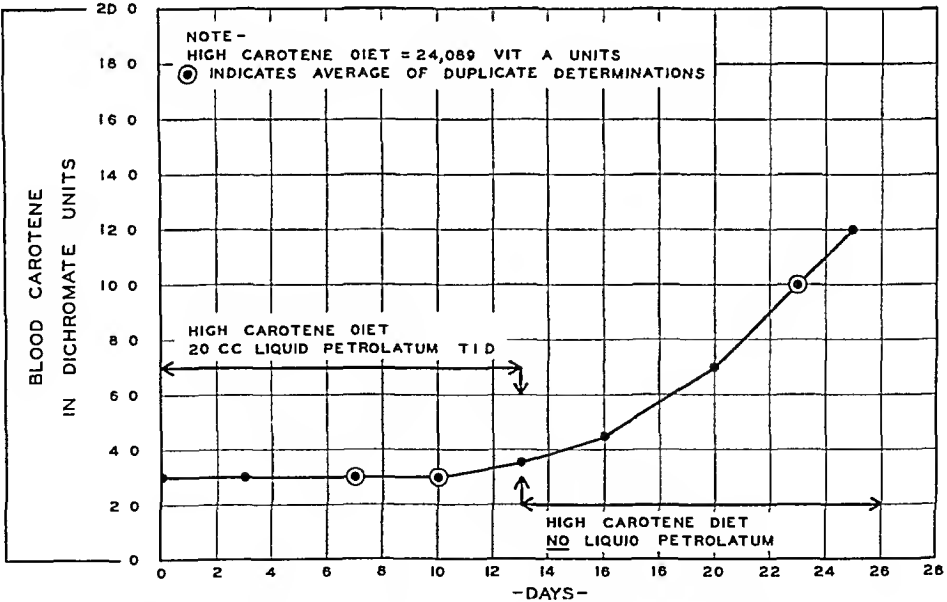


Chart 3—Effect of 20 cc of liquid petrolatum taken three times daily before meals on the blood carotene of a patient on a high carotene diet. During the period when the liquid petrolatum was taken the blood carotene level remained constant. When the liquid petrolatum was omitted and the diet continued, the blood carotene level rapidly increased.

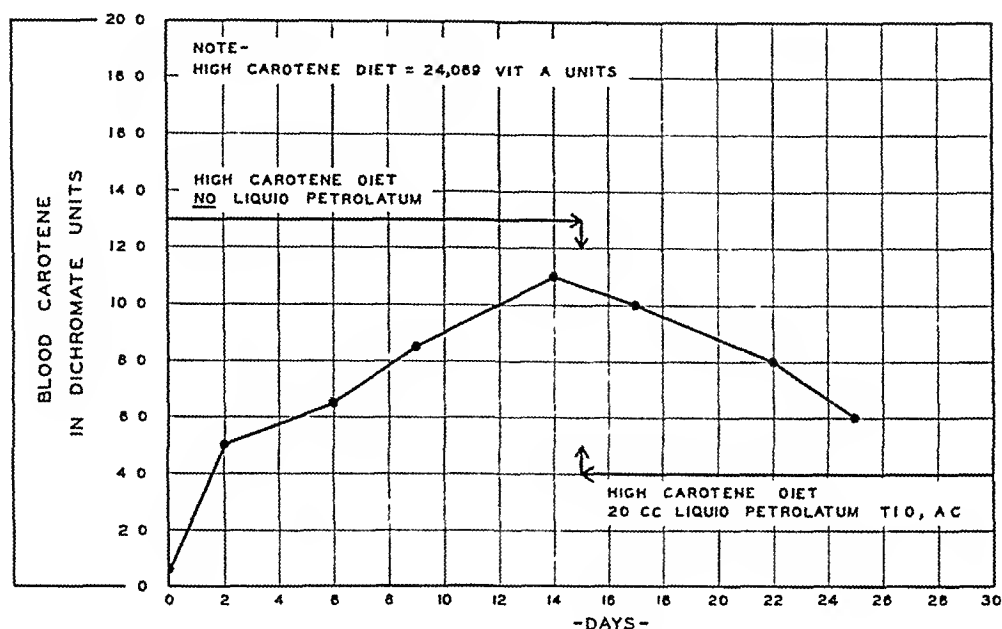


Chart 4—Rise in the blood carotene of a patient on a high carotene diet and its subsequent fall when 20 cc of liquid petrolatum was given three times daily before meals

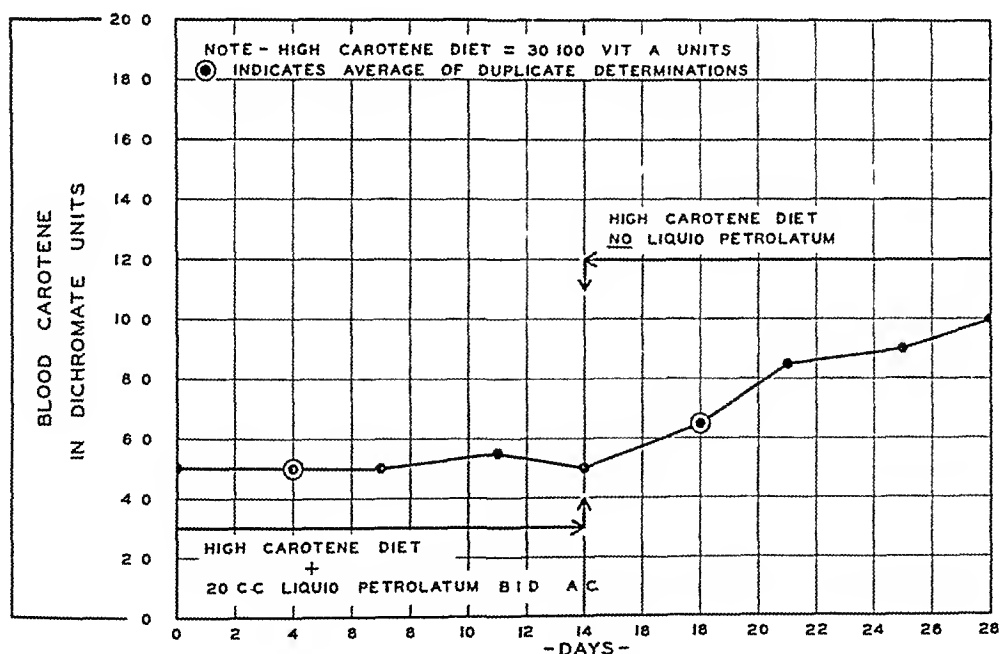


Chart 5—Effect of 20 cc of liquid petrolatum taken twice daily (before the morning and evening meals) on a patient eating a high carotene diet. The blood carotene remained constant as long as the mineral oil was taken. When the liquid petrolatum was omitted, the blood carotene level rapidly increased.



This experiment is admittedly an artificial one. The average human being does not take carotene as a mixture of crystalline carotene dissolved in liquid petrolatum. Our object in planning the experiment this way was to see whether Jackson's<sup>5</sup> results, showing a greater absorption of carotene by liquid petrolatum when the latter was mixed with carotene-bearing foods, could be duplicated in human beings.

After obtaining decided variation in the blood content of carotene by the administration of liquid petrolatum to an otherwise high carotene mixture, we devised experiments to imitate more closely the manner in which liquid petrolatum was ordinarily given and thus to see what effect the petrolatum might have when all of the carotene was in natural form. Chart 3 shows that if a patient followed a high carotene diet and took

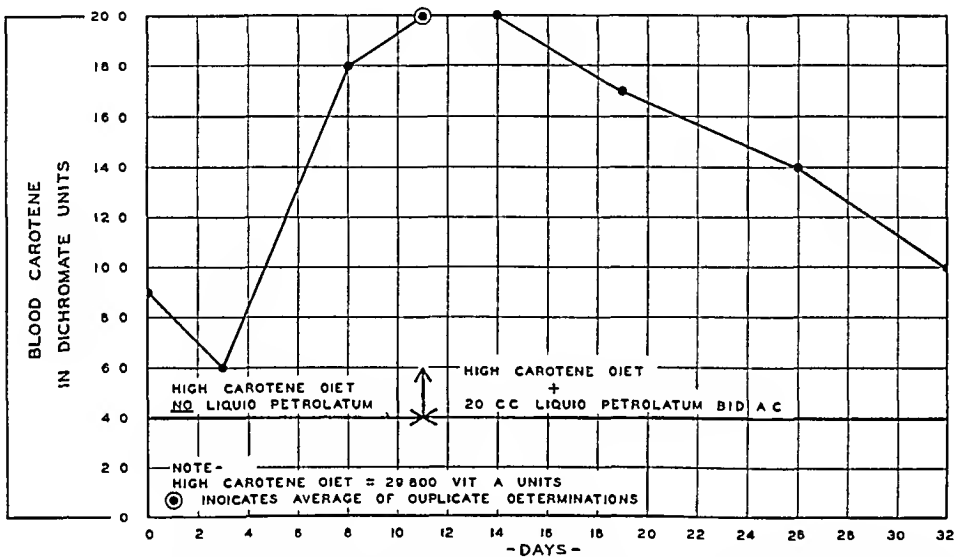


Chart 6—Rise in the blood carotene of a patient on a high carotene diet and its subsequent fall when 20 cc of liquid petrolatum was given twice daily, before the morning and evening meals

20 cc of liquid petrolatum before meals, the blood carotene stayed at a constant level. If the diet was continued but the liquid petrolatum omitted, a rapid rise in blood carotene occurred. Chart 4 shows the rise in blood carotene which occurred when a high carotene diet was fed alone and the subsequent fall in blood carotene when 20 cc of liquid petrolatum was given before meals.

When 20 cc of liquid petrolatum was given twice daily, before the morning and the night meals, to patients on high carotene diets, the effect on the blood carotene was still definite, as may be seen in charts 5 and 6.

When 30 cc of liquid petrolatum was given before retiring, the upper part of the gastrointestinal tract was probably empty and there-

fore little opportunity existed for mixture of the petrolatum with food Chart 7 A shows that the blood carotene rose in spite of the liquid petrolatum and that it continued to rise when the liquid petrolatum was stopped Chart 7 B shows that the administration of 30 cc of liquid

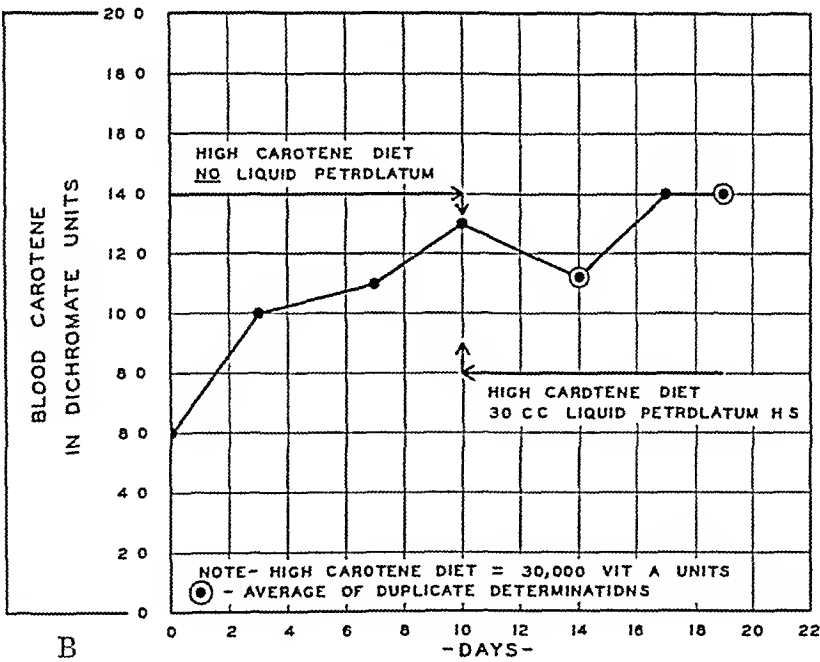
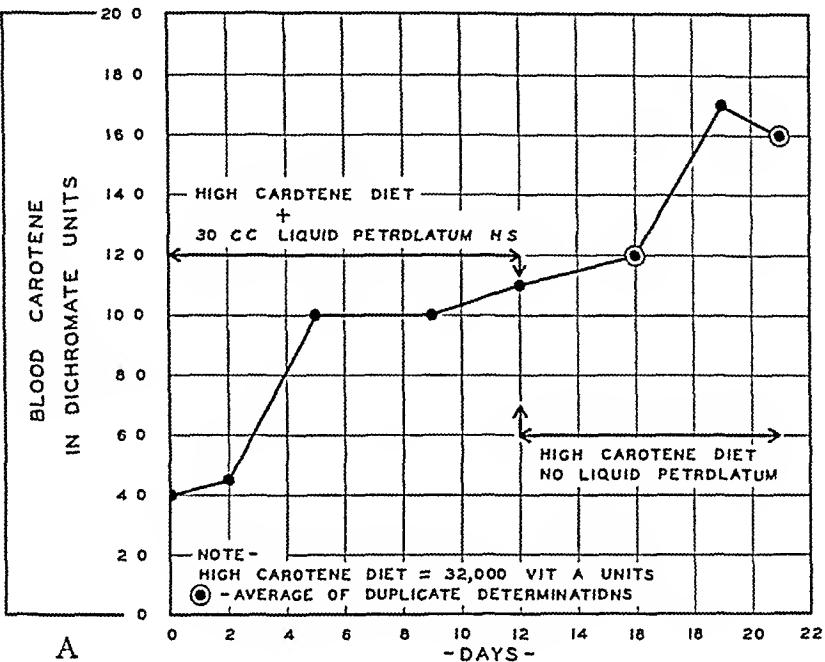


Chart 7—When 30 cc of liquid petrolatum was given to patients on a high carotene diet just before retiring, little opportunity existed for mixture of the oil and food, and little if any diversion of the carotene occurred, as measured by the blood carotene levels

petrolatum to a patient on a high carotene diet caused little if any diversion of the carotene

## COMMENT

It will be seen in the previous experiments that liquid petrolatum given in amounts of 20 cc three times daily or twice daily before meals, or mixed with carotene dissolved in cottonseed oil, prevents complete absorption of carotene from the ingested material. In this respect, these experiments compare with those previously quoted of Dutcher and his colleagues, of Mitchell and of Jackson.

A comparison of charts 3 and 5 shows that the rise of blood carotene is much more rapid when carotene is fed dissolved in vegetable oil than when a diet containing large amounts of carotene is given. It is also evident that the fall in blood carotene is much more rapid when fed in this manner, mixed with liquid petrolatum, than when liquid petrolatum and high carotene foods are given. The total number of vitamin A units is somewhat greater when 3 cc of carotene in oil is fed daily with a low carotene diet (25,458 units) than when a high carotene diet alone is fed (24,089 units). This slight difference may explain the more rapid rise in blood carotene, but it does not explain its rapid fall. The mixture of the carotene in oil with liquid petrolatum must then be responsible for this change. We believe these experiments confirm Jackson's<sup>5</sup> conclusion that a greater depletion of carotene occurs when carotene foods and liquid petrolatum are mixed than when they are fed separately.

When the total amount of liquid petrolatum is decreased from 60 cc daily to 40 cc daily but the oil is still given in 20 cc doses before the morning and the night meal, the diversion of carotene seems to be as pronounced as when 20 cc is given three times daily. When a total of 30 cc of liquid petrolatum is given to a patient on an apparently "empty" stomach, there seems to be little if any effect on the absorption of carotene from the gastrointestinal tract, as measured by the blood carotene.

Carotene cannot be regarded as vitamin A, and we do not wish to infer that our determinations are of anything but carotene. The vitamin is formed in the animal body from its precursors, the carotenes, or is ingested in pure form in the products of other animals. Because of the existing relationship between vitamin A and carotene, the level of the blood carotene should reflect to some degree the amount of available vitamin A present. For the same reason any substance which will prevent the absorption of carotene from the gastrointestinal tract will indirectly diminish the available vitamin A of the body.

In the experiments presented here, the amount of carotene available in the diets or in the carotene in oil was several times greater than that required, and the amounts of liquid petrolatum given in the first experiments were slightly more than average. The administration of liquid

petrolatum immediately before meals is not the customary manner of using the drug therapeutically, but some physicians prescribe it that way, believing it has a better effect as a laxative when so used. The administration of liquid petrolatum just before retiring is the common method of prescribing it. We do not wish to imply that all the conditions which have been demonstrated in this study necessarily exist in the ordinary use of the drug, but we do believe that if liquid petrolatum is administered at a time of the day when it may be mixed with food in the gastrointestinal tract it interferes with the absorption of carotene.

#### CONCLUSIONS

1 When crystalline carotene is fed in vegetable oil to persons on a constant diet, an elevation of the blood content of carotene is demonstrated.

2 When liquid petrolatum is added to the mixture, there is a reversal of this effect.

3 Liquid petrolatum in amounts of 20 cc three times daily before meals or 20 cc twice daily before meals abolishes or reverses the response of the blood carotene to a high carotene diet.

4 Little if any effect on the blood carotene is demonstrated when the liquid petrolatum is given in a single dose of 30 cc at bedtime.

# GASTRIC BARRIER IN BACILLARY DYSENTERY

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NEW YORK

In epidemiologic studies of bacillary dysentery one is often confronted by the problem of why some exposed persons contract the disease while others escape infection. This fact is particularly surprising during outbreaks definitely traceable to a common source, such as contaminated food or water. Although natural or acquired immunity to the disease may be present in isolated instances, it can hardly be the sole explanation, since a low percentage of immunity among exposed persons during epidemics appears to be so general. Moreover, the viability and antigenic specificity of the dysentery organism can often be demonstrated in the contaminated food which has been ingested by affected and by unaffected persons alike. The explanation obviously lies in some protective mechanism of the body, and since the gastric juice offers the first barrier to the swallowed dysentery organisms a study of this factor was undertaken.

The role of the gastric secretion in preventing the passage of bacteria from the mouth to the intestine has been studied intensively by Arnold and his associates<sup>1</sup>. They have shown that as long as free hydrogen ions are present within the gastric lumen, few viable bacteria are to be found there. Swallowed oral bacteria survive in the stomach when the  $p_H$  is more alkaline than 3. Thus in patients with a deficiency of acid secretion the oral flora extends from the lips to the pylorus. A normally functioning gastric mucosa produces a secretion which saturates the ingested food with acid radicals. Arnold has stated that the contents of the duodenum and jejunum have a  $p_H$  range of 5 to 6.5, depending largely on the effectiveness of the acid saturation in the stomach. The figures as stated indicate a good acidifying gastric mechanism, the duodenal flora being represented by a few enterococci. There appears to be a close relation, therefore, between the gastric and the duodenal secretion in the control of bacterial flora.

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This investigation was aided by a grant from the Blood Betterment Association

1 Arnold, L. J. Infect. Dis. **38** 246, 1926, Am. J. Pub. Health **17** 918, 1927, Host Susceptibility to Typhoid, Dysentery, Food Poisoning and Diarrhea, J. A. M. A. **89** 789 (Sept. 3) 1927, Am. J. Hyg. **8** 604, 1928, J. Hyg. **29** 82, 1929. Hood, M., and Arnold, L. Am. J. Digest. Dis. & Nutrition **4** 40 and 95, 1937. Arnold, L., and Brody, L. Am. J. Hyg. **6** 672, 1926.

In addition to the acid protective mechanism of the stomach, Florey<sup>2</sup> has stressed the important role which is played by the mucous secretion. Nonpathogenic bacteria are enmeshed in the mucus and rendered inert. Those which are sensitive to lysozyme are dissolved. Pathogens such as *Bacillus typhi murium*, however, appear to elicit in the intestine a migration of phagocytic cells into the lumen, with the production of focal areas of mucosal denudation.

In studying the bactericidal effect of gastric juice, a dysentery strain was chosen which has been the source of many outbreaks of gradually increasing frequency and severity.

#### MATERIAL AND METHOD

Gastric contents were obtained from the specimens submitted for routine gastric analysis in the hospital. In the great majority of instances only specimens obtained during fasting were used for the test, while in others, specimens taken for fractional analysis after an Ewald test meal were utilized. Throughout the procedure a single strain of *Bacillus dysenteriae* was used as a measure of the bactericidal action, namely, the Sonne-Duval (D) strain. This strain was obtained from the Department of Health of the city of New York and conformed to all the usually accepted criteria for the Sonne-Duval strain. The organism was a gram-negative, nonmotile, nonspore-forming, aerobic rod which produced acid but no gas in the following carbohydrates: dextrose, galactose, mannitol, maltose, rhamnose and lactose. In the last three substances named, acid was formed only after three or four days' incubation. No change was produced in salicin, sucrose or xylose. In litmus milk there was slight production of acid. Tests for indole in peptone water cultures gave positive results. Serologically, this strain agglutinated with Mount Desert serum to a titer of 1:2,560 and with Sonne-Duval serum to a titer of 1:10,240.

The method used in testing the inhibitory action of gastric contents for this strain of *B. dysenteriae* was, briefly, as follows. The material when received was immediately passed through a Seitz bacterial filter and cultured for sterility. To 2 cc. of the sterile gastric filtrate was added 0.25 cc. of a standardized eighteen hour broth culture ( $p_H$ , 7) of the Sonne-Duval strain of *B. dysenteriae*. In every instance a saline control was used. The  $p_H$  of the gastric filtrate was determined by the colorimetric method, standard buffer solutions being used with the following indicators: thymol blue ( $p_H$  range, 1.2 to 2.8), bromphenol blue ( $p_H$  range, 3 to 4.6), methyl red ( $p_H$  range, 4.4 to 6) and bromthymol blue ( $p_H$  range, 6 to 7.6). On the addition of the culture, the filtrates were incubated at 37.5 C., and subcultures were made after fifteen, thirty, sixty and one hundred and twenty minutes. The tubes were then permitted to remain in the incubator over night, and subculture was again carried out, to determine whether the inhibition might possibly be transitory. In no case was this evident.

#### RESULTS

*Growth in Filtered Gastric Juice*—In table 1 are summarized the results of fifty tests performed to determine the effect of filtered human

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<sup>2</sup> Florey, H. W. J. Path. & Bact. **37**: 283, 1933.

gastric juice on the strain of *B. dysenteriae* employed. A study of the figures reveals that every specimen having a  $p_H$  of 5.5 or lower completely inhibited the growth of the test organism. The specimens included in these  $p_H$  values (i. e., a  $p_H$  of 5.5 or less) showed a range of free hydrochloric acid from 16 to 93. In several instances (tests 21,

TABLE 1—Summary of Fifty Studies Indicating the Bactericidal Effect of Filtered Human Gastric Juice on the Sonne-Duval D Strain of *B. Dysenteriae* \*

Growth						Growth					
No	$p_H$	After 15 Min	After 30 Min	After 60 Min	After 120 Min	No	$p_H$	After 15 Min	After 30 Min	After 60 Min	After 120 Min
1	41	0	0	0	0	26	67	++++	++++	++++	++++
2	37	0	0	0	0	27	67	++++	++++	++++	++++
3	49	0	0	0	0	28	70	++++	++++	++++	++++
4	29	0	0	0	0	29	68	++++	++++	++++	++++
5	74	++++	++++	++++	+++	30	68	++++	++++	++++	++++
6	66	++++	+	0	0	31	33	0	0	0	0
7	76	++++	++++	++++	+++	32	52	+	0	0	0
8	40	0	0	0	0	33	70	++++	++++	++++	++++
9	44	0	0	0	0	34	28	0	0	0	0
10	48	0	0	0	0	35	65	++++	++++	++++	++++
11	27	0	0	0	0	36	60	++++	++++	++++	++++
12	50	0	0	0	0	37	72	++++	++++	++++	++++
13	50	0	0	0	0	38	32	0	0	0	0
14	67	++++	++++	++++	++++	39	48	0	0	0	0
15	72	++++	++++	++++	++++	40	52	0	0	0	0
16	36	0	0	0	0	41	36	++++	+++	+++	0
17	40	0	0	0	0	42	40	0	0	0	0
18	36	0	0	0	0	43	31	+	0	0	0
19	50	0	0	0	0	44	34	0	0	0	0
20	34	0	0	0	0	45	60	0	0	0	0
21	34	+	0	0	0	46	38	0	0	0	0
22	36	0	0	0	0	47	35	0	0	0	0
23	74	++++	++++	++++	++++	48	25	++++	++	0	0
24	29	0	0	0	0	49	34	++	+	0	0
25	73	++++	++++	++++	++++	50	40	0	0	0	0

\* In this table and in the succeeding tables, the symbols are used as follows: 0 indicates no growth on agar plate, +, infrequent scattered colonies on an agar plate, ++, a greater number of colonies but no confluent growth, +++, some confluent growth with some scattered colonies, and +++++, confluent growth, with no individual colonies.

TABLE 2—Bactericidal Effect of Sixty Gastric Filtrates as Related to the  $p_H$  Values

$p_H$	Growth	No Growth
2.5-3.0	0	8
3.1-3.5	0	10
3.6-4.0	0	11
4.1-4.5	0	5
4.6-5.0	0	7
5.1-5.5	0	2
5.6-6.5	2	1
6.6-7.0	6	1
7.1-7.6	7	0

41, 48 and 49) the inhibition manifested itself only after prolonged contact between the gastric filtrate and the organism. With a rise in the  $p_H$  above 5.5 and therefore a lower acidity, the germicidal activity began to disappear to the extent that above a  $p_H$  of 6 the growth of the organism was not at all affected by the presence of the gastric filtrate. Table 2 presents these results in a more concise form and also indicates the complete cessation of growth at the stated  $p_H$  values.

The  $p_H$  determinations in our series ranged from 2.5 to some which were slightly alkaline. The limited series and the possibility of a slight regurgitation of bile into the pylorus might be considered as factors accounting for some of the high  $p_H$  values obtained for the gastric filtrates.

In an earlier study Bartle and Harkins<sup>3</sup> found that when the free hydrochloric acid content of gastric juice was less than 10, no germicidal activity could be demonstrated. However, with a free hydrochloric acid content ranging from 20 to 100 (corresponding to  $p_H$  values of approximately 5.5 or less), there was definite bactericidal action. Despite a difference in the actual technic, our results parallel quite closely those obtained by these authors. This is illustrated in tables 1 and 2.

*Growth in Buffer Acid Solutions*—Since our studies with the gastric filtrates indicated a fairly sharp delimitation beyond which the dysentery

TABLE 3—Effect of Buffer Acid Solutions on the Growth of the Sonne-Duval D Strain

Growth					Growth				
$p_H$	After 15 Min	After 30 Min	After 60 Min	After 120 Min	$p_H$	After 15 Min	After 30 Min	After 60 Min	After 120 Min
2.2	0	0	0	0	4.1	0	0	0	0
2.6	0	0	0	0	4.4	+	0	0	0
2.8	0	0	0	0	4.5	+	0	0	0
3.0	0	0	0	0	4.8	++	++	+	+
3.4	0	0	0	0	5.2	++++	++++	++++	++++
3.7	0	0	0	0	5.6	++++	++++	++++	++++
3.8	0	0	0	0	6.0	++++	++++	++++	++++
4.0	0	0	0	0	Saline	++++	++++	++++	++++

organism ceased to grow, it was of interest to determine the comparative inhibitory action of buffer acid solutions. Utilizing the same technic, the growth of *B. dysenteriae* in solutions of known  $p_H$  was studied.

The solutions were prepared by adding fifth-normal hydrochloric acid or sodium hydroxide to fifth-molar acid potassium phthalate in amounts giving the  $p_H$  values designated in table 3. The  $p_H$  of each solution was checked by the colorimetric method. This study was repeated on two occasions with freshly prepared solutions that were passed through Seitz filters.

Examination of the data reveals that the Sonne-Duval (D) strain of *B. dysenteriae* will not grow after contact with a solution having a  $p_H$  of 4.5 or less. At a slightly lower acidity the inhibition is only partly demonstrable, but beyond this point the organism flourishes. This characteristic may be termed the acid tolerance of the strain, and it corroborates the generally accepted limits beyond which this group of bacteria will not survive. For the Flexner Y and Shiga strains similar results were noted. These strains will grow in acid solution having a



$p_H$  value of 4.4 or greater. The acid tolerance of many strains of *Bacillus coli* has been set at a  $p_H$  of 4.6. The close correlation found for the inhibitory action of gastric juice and of inorganic acids has been previously reported by Knott<sup>4</sup> and also by Bartle and Harkins<sup>3</sup>.

A comparison of the results obtained in the two studies indicates that the hydrogen ion concentration may not be the sole operating factor which determines the bactericidal power of gastric juice. This thought is usually implied, however, when the barrier of gastric juice to the passage of bacteria is considered. The possibility that a variety of factors may determine the effectiveness of this barrier is further indicated by the difference in the levels of acidity at which *B. dysenteriae* will survive in gastric juice as compared with buffer acid solutions.

*Growth in Buffer Acid Solutions with the Addition of Pepsin*—This study was prompted by the desire to determine the viability of *B. dysen-*

TABLE 4—*The Effect of Buffer Acid Solutions with Added Pepsin on the Growth of the Sonne-Duval D Strain*

Growth					Growth				
$p_H$	After 15 Min	After 30 Min	After 60 Min	After 120 Min	$p_H$	After 15 Min	After 30 Min	After 60 Min	After 120 Min
2.2	0	0	0	0	4.4	++++	++++	++++	++++
2.6	0	0	0	0	4.8	++++	++++	++++	++++
3.0	0	0	0	0	5.2	++++	++++	++++	++++
3.4	+++	++	0	0	5.6	++++	++++	++++	++++
3.8	++++	++++	++++	++	6.0	++++	++++	++++	++++
4.0	++++	++++	++++	++++	Saline	++++	++++	++++	++++

teriae in the presence of the gastric enzyme and of buffer acid solutions. Utilizing the solutions and setup described in table 3, but with the addition of pepsin, the previous experiment was repeated. Commercial pepsin was added to each  $p_H$  solution in amounts sufficient to result in a final concentration of 0.75 per cent pepsin in each tube. Table 4 details the setup and the results obtained. The addition of the pepsin seemed, in this instance, to enhance the growth of the bacteria at  $p_H$  values at which, with only acid solutions present, complete inhibition had been obtained. The precise reason for this cannot be stated definitely at present, but the purely physical action of the added protein in the form of pepsin may be considered a factor. In this connection the work of Nungester, Jourdonais and Wolf<sup>5</sup> is of interest. These authors found that the use of mucin as a menstruum for bacteria greatly increases the invasive powers of the organisms. They also suggested that the viscosity and cohesiveness of the mucin appear to be important factors.

4 Knott, F. A. Guy's Hosp. Rep. **73**: 429, 1923.

5 Nungester, W. J., Jourdonais, L. F., and Wolf, A. A. J. Infect. Dis. **59**: 11, 1936.

The question arises, then Does the presence of pepsin facilitate the germicidal activity of gastric juice in those instances in which sufficient hydrogen ions are available? Schonbauer<sup>6</sup> answered definitely in the affirmative, while Knott concluded that in comparison with the action of free hydrochloric acid, the peptic activity of gastric juice is seemingly unimportant The latter view is also upheld in the work of Arnold and his associates, who found that the gastric acidity is directly responsible and is the major factor in determining the efficacy of the gastric barrier

To study the point further we tested both the bactericidal action and the peptic activity of ten samples of gastric contents The  $p_H$  values were also determined For the estimation of pepsin in the gastric filtrates the edestin method was used Table 5 contains the results of

TABLE 5—*Summary of the Bactericidal Properties of Ten Gastric Filtrates and Their Peptic Activity*

Filtrate Number	$p_H$	Growth				Pepsin Gastric Juice*
		After 15 Min	After 30 Min	After 60 Min	After 120 Min	
51	2.9	0	0	0	0	1.080
52	2.7	0	0	0	0	1.078
53	3.0	0	0	0	0	1.074
54	3.5	+++	++	+	0	1.066
55	4.0	0	0	0	0	1.080
56	4.6	+	0	0	0	1.089
57	3.2	0	0	0	0	1.010
58	4.4	0	0	0	0	1.180
59	4.2	0	0	0	0	1.200
60	4.5	0	0	0	0	1.200

\* The figures indicate the relative values of pepsin in the standard control, as 1, and the amount found in the gastric juice

this series of tests, and it is readily seen that the results parallel those obtained with the original fifty specimens Specimen 54 is worthy of some note The  $p_H$  of this specimen was 3.5 From the previous figures, complete inhibition would have been expected in this case as in all others in which there was a similar  $p_H$  value Actually, the inhibition became manifest only after one hundred and twenty minutes of incubation A glance at the table indicates, however, that this specimen showed peptic activity approximating only 5 to 10 per cent of the amount found in the other specimens No broad conclusions can be drawn, but continued studies along this line are suggested by these observations

#### COMMENT

It is possible that in the human body the infectivity of dysentery organisms is determined primarily by the degree of acidity in the stomach at the time of their ingestion In the normal state, psychic and chemical

6 Schonbauer, cited by Bartle and Harkins<sup>3</sup>

stimuli determine the amount of gastric secretion. The curve for fasting and postprandial acid is an additional factor. In pathologic states there may be complete anacidity or a  $p_H$  concentration above the level which will completely inhibit or kill the dysentery organism. The mechanical protective action against the bacilli offered by food, the emptying time of the stomach and the point in the digestive cycle at which the organisms enter the stomach are undetermined factors which must influence any deductions that may be drawn from our studies.

#### CONCLUSIONS

1. Filtered human gastric juice is bactericidal for the Sonne-Duval (D) strain of *B. dysenteriae* when the  $p_H$  is approximately 5.5 or less.

2. Similar action is demonstrable with acid solutions having  $p_H$  values of 4.5 or less.

3. The addition of pepsin to buffer acid solutions impedes their bactericidal effect.

4. From the limited series presented it may be inferred that the hydrogen ion concentration is chiefly responsible for the bactericidal action of gastric juice in the case of *B. dysenteriae*.

5. The possible application of these observations to the infectivity of *B. dysenteriae* in human beings is suggested.

# STUDIES IN EXOPHTHALMIC GOITER

## I ITS INCIDENCE THROUGHOUT THE UNITED STATES

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More than a century of study and treatment of exophthalmic goiter has failed to reveal its cause. The internist, the surgeon and the roentgenologist have each made contributions to the clinical knowledge of this disease, chiefly in the field of therapy. But the advances which have refined their therapy were born necessarily of empiricism. These advances, moreover, although extensively applied and wisely evaluated, have yielded no clue as to etiology. The surgeon and the pathologist have joined forces to lift the veil of mystery from this disease. The physiologist and the biochemist have lent their aid. Yet the etiology of exophthalmic goiter is still unknown. The statement is as true today as it was in 1883, when said by Pierre Marie of this strange malady, "There are in pathogenesis, as in therapy, many theories but little truth."

Pursuit of the etiology of exophthalmic goiter has been hampered because this disease neither occurs spontaneously in animals nor can be reproduced experimentally in its entirety. Recently, however, there has been made in the experimental field some progress which gives promise of advancing the knowledge of its pathogenesis.

From an etiologic point of view it is surprising that after one hundred years so little is known positively about the conditions which favor the development of this disease. It has been stated that exophthalmic goiter, like certain neuroses, affects only civilized man, and also that some human races are immune to it. Probably these statements are only half-truths. Twenty-one years ago Robert McCarrison<sup>1</sup> wrote

We know little of the climatic or geographical distribution of exophthalmic goiter, of the influence of race, of season, of altitude, of its prevalence in town or country, of its incidence among the rich and poor. It is stated to be more common at the sea-coast than inland, but this is an impression only. It is, however, very rare in regions where goiter is endemic.

Conflicting statements as to the role played by the thyroid gland in this disease are found in the literature. Life-long students of diseases

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1 McCarrison, R. The Thyroid Gland in Health and Disease, London, Baillière, Tindall & Cox, 1917, p 195

of the thyroid express diametrically opposed opinions as to the relation of endemic goiter to so-called exophthalmic goiter. Besides McCarrison, already quoted, Bircher,<sup>2</sup> von Mueller,<sup>3</sup> Kocher,<sup>4</sup> Berry,<sup>5</sup> Aschoff<sup>6</sup> and others have stated that exophthalmic goiter is just as common in goiter-free districts as it is in regions where goiter is endemic. On the other hand, Crotti in this country, Feldman in Germany, Vomela in Montenegro<sup>7</sup> and other investigators have stated that they find toxic goiter much more frequent in districts of endemic goiter. The most recent report on this disputed question is a statistical study made by Sallstrom,<sup>8</sup> who found that in Sweden, at least, toxic and endemic goiter are unrelated as to incidence.

More pertinent to physicians in this country and to this report, is the work of McClendon and Hathaway,<sup>9</sup> who in 1924 reached a conclusion just opposite to that of Sallstrom. They published the results of analyses of food and water from various parts of the United States, constructing a map which showed the iodine-rich and iodine-poor sections of the country. They also published maps showing the incidence of simple goiter and of exophthalmic goiter, based on data from the United States Army Draft Board. The similarity in the maps led the authors to claim "We consider that we have proved statistically that both simple and exophthalmic goiter in the United States are caused by iodine starvation."

That this startling statement has been accepted without question by some investigators is revealed by a recent concurring reference<sup>10</sup> to the work of McClendon and Hathaway. Their sweeping conclusion, nevertheless, is open to criticism on several grounds. From a statistical point of view alone, the sampling seems inadequate, because their data were derived from a relatively small population which is exclusively

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2 Bircher, cited by McCarrison<sup>1</sup>

3 von Mueller, F. Problems of Endemic Goiter, *Ann Int Med* **10** 1617 (May) 1937

4 Kocher, T., cited by von Mueller<sup>3</sup>

5 Berry, J. Diseases of the Thyroid Gland and Their Surgical Treatment, London, J & A Churchill, 1901, p 177

6 Aschoff, L. Ueber das Vorkommen der Basedow-Schilddrüse in Japan, *München med Wchnschr* **81** 902 (June 15) 1934

7 Cited in Comparative Geography of Thyrotoxicosis, editorial, *J A M A* **106** 216 (Jan 18) 1936

8 Sallstrom, T. Vorkommen und Verbreitung der Thyrotoxicosis in Schweden, Stockholm, 1935

9 McClendon, J F, and Hathaway, J C. Inverse Ratio Between Iodine in Food and Drink and Goiter, Simple and Exophthalmic, *J A M A* **82** 1668 (May 24) 1924

10 McClure, R D. The Incidence of Operations for Goiter in Southern Michigan. Effect of Iodized Salt After Twelve Years' General Use, *J A M A* **109** 782 (Sept 4) 1937

male and which is limited as to age. Also it seems unlikely that exophthalmic goiter in this country differs from the same disease elsewhere in the world, and certainly it has long been recognized that exophthalmic goiter (Graves's disease, Basedow's disease, Flajani's disease, etc.) is not confined to goitrous areas<sup>11</sup>. It is encountered in every land and clime and in practically every race. These general impressions should be supplemented, however, by more exact knowledge of the influence of racial, geographic, geologic and climatic factors<sup>12</sup> as well as of other environmental influences on the incidence of the disease. Statistical studies have yielded valuable information about other diseases, and it seems possible that this method of approach to exophthalmic goiter might aid in attaining a better understanding of the etiology of this disease.

The United States affords a suitable sample area for the study of some of the factors mentioned. It contains about one thirtieth of the earth's population, embraces two long coast lines, two great mountain chains, large rivers and inland valleys, desert areas and great lakes. It includes at least two goitrous regions. Its white population is as cosmopolitan as that of any similar large area. It has a small native Indian population and a moderate number of Orientals, and about one tenth of its total population is Negro. This racial variety makes possible the investigation of other aspects of the problem, on which I shall report at a later date.

#### ENDEMIC GOITER

In beginning a study of exophthalmic goiter, it seems advisable in this first report to ascertain as exactly as possible the respective incidences of endemic and of so-called exophthalmic goiter in the United States. A fairly accurate estimate of the distribution of endemic goiter is gained from Olesen's<sup>13</sup> data, published by the United States Public Health Service in 1929. From these was constructed figure 1, which shows the incidence of simple goiter throughout the country.

#### EXOPHTHALMIC GOITER

For the reasons already given, draft statistics do not furnish adequate figures for estimating the frequency of exophthalmic goiter. Therefore, to ascertain the incidence of this disease I sent 1,300 questionnaires to the larger hospitals of the country to inquire, among other

11 Comparative Geography of Thyrotoxicosis, editorial, J. A. M. A. **106** 216 (Jan. 18) 1936.

12 Mills, C. A. Climate as a Potential Factor in the Etiology of Exophthalmic Goiter and Other Metabolic Diseases, *Endocrinology* **16** 52 (Jan.-Feb.) 1932.

13 Olesen, R. Distribution of Endemic Goiter in the United States as Shown by Thyroid Surveys, *Pub. Health Rep.* **44** 1463 (June 21) 1929.

things, the total admissions for the preceding ten years and the number of cases of conditions diagnosed as exophthalmic goiter, hyperthyroidism, etc. Over four hundred hospitals sent the data requested. While I realize that this method involves the diagnostic errors inherent in every survey for morbidity or mortality, as well as other inaccuracies (some of which counterbalance), nevertheless by large geographic grouping there is obtained as fair an estimate of the incidence of exophthalmic goiter in the United States as has yet been reported.

The result of this survey for morbidity is shown in table 1 and in figure 2. It will be seen from the table that the mean incidence of

TABLE 1—*Incidence of Exophthalmic Goiter in the United States*

Region	States Included	Number of States	Number of Hospitals Reporting	Total Hospital Admissions	Patients with Exophthalmic Goiter		Mortality, Per centage
					Number	Percentage	
North Atlantic	Conn., Maine, Mass., N. H., N. J., N. Y., Pa., R. I., Vt.	9	114	5,564,383	27,609	0.50	0.19
North Central	Ill., Ind., Iowa, Meh., Minn., Neb., N. D., Ohio, S. D., Wis.	10	103	3,507,843	27,011	0.77	0.44
Southern	Ala., Ark., Fla., Ga., La., Miss., N. C., Okla., S. C., Tenn., Texas, Va.	12	92	1,878,000	4,884	0.26	0.10
Border States	Del., D. C., Kan., Ky., Md., Mo., W. Va.	7	51	1,213,308	7,188	0.59	0.24
Rocky Mountain	Colo., Idaho, Mont., N. Mex., Utah, Wyo.	6	25	317,643	2,800	0.88	0.29
Pacific Northwest	Ore., Wash.	2	14	285,337	4,711	1.65	0.48
Pacific Southwest	Ariz., Calif., Nev.	3	43	1,328,516	5,316	0.40	0.19
Total		49	442	14,095,030	79,519		
Mean per cent						0.57	0.26

\* Figures in the last column, taken from the United States Mortality Reports, are given for comparison.

exophthalmic goiter in 14,000,000 hospital admissions was 0.57 per cent. I am under no delusions regarding the accuracy of this figure and realize that it can be only an approximation. From the nature of this survey it was impossible to eliminate the error caused by readmission of the same patient. The slight increase due to this statistical error is probably counterbalanced by failure to diagnose the condition correctly when it occurred in some of its more obscure forms. In general, however, the figure for percentage incidence of exophthalmic goiter would seem to be slightly more accurate than that for other diseases more difficult to diagnose.

As an independent check on my data I constructed another map (fig. 3) from the United States Mortality Statistics for the thirteen

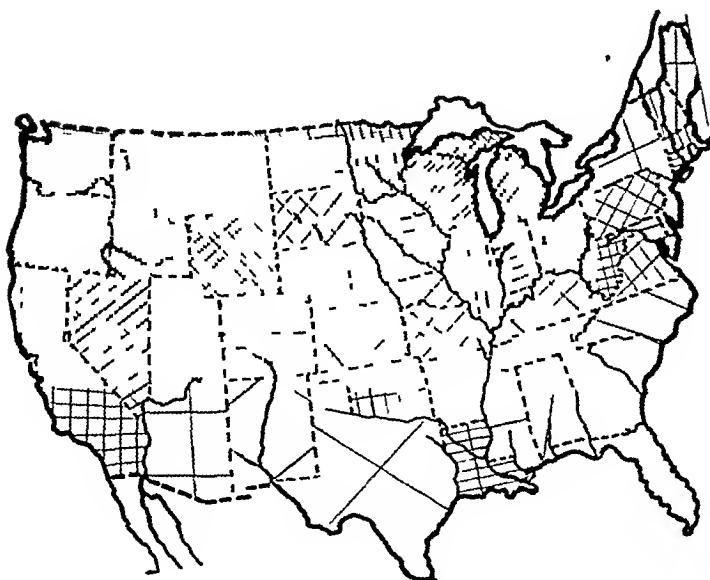


Fig 1—Incidence of simple goiter in the United States This map is a composite of (1) Olesen's<sup>13</sup> map based on over two and a half million examinations of men for military service and (2) a map constructed from Olesen's<sup>13</sup> collection of various surveys, made chiefly in schools State and geographic boundaries seldom coincide, and the sharp distinctions are artificial, but an approximation of the relative frequency of endemic goiter is obtained Arkansas, Georgia, South Carolina and Florida had incidences too low to rate even one line on the scale used here The lines showing mortality are at right angles to those representing morbidity, so that when superimposed photographically each state appears cross hatched

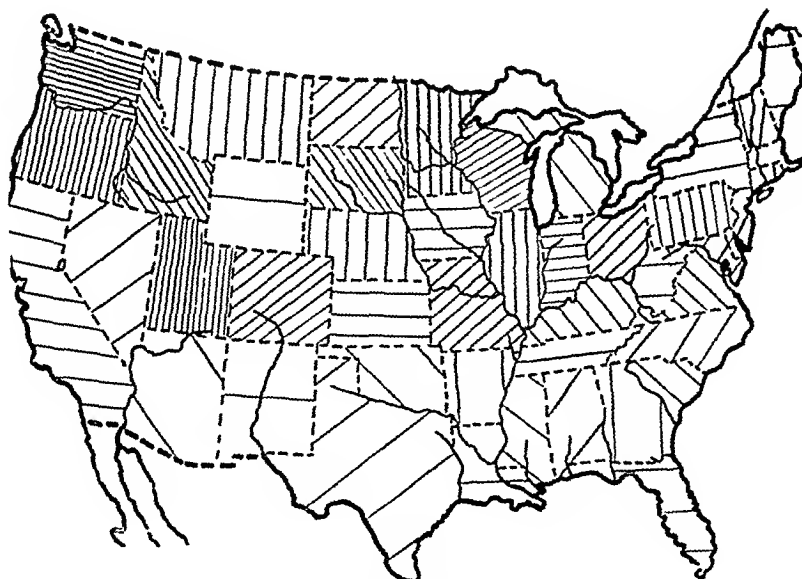


Fig 2—Morbidity from exophthalmic goiter in the United States, based on reports of four hundred and forty-two hospitals in forty-eight states and the District of Columbia The majority of reports covered the decade from 1925 to 1934



years 1920 to 1932. Since 1920, deaths from exophthalmic goiter have been reported for the Registration Area, which also since that time has included most of continental United States. The similarity in the maps representing morbidity and mortality is evident, but to obtain a truer picture of the incidence of exophthalmic goiter in the different regions of this country the two maps were combined by photographic superposition to make figure 4.

By comparing figure 1 with figure 4, one can see the relative incidence of endemic and exophthalmic goiter. While there is a general similarity between the two maps, it is apparent that exophthalmic goiter occurs with greater uniformity throughout the country than does simple or endemic goiter. These maps show a greater tendency for

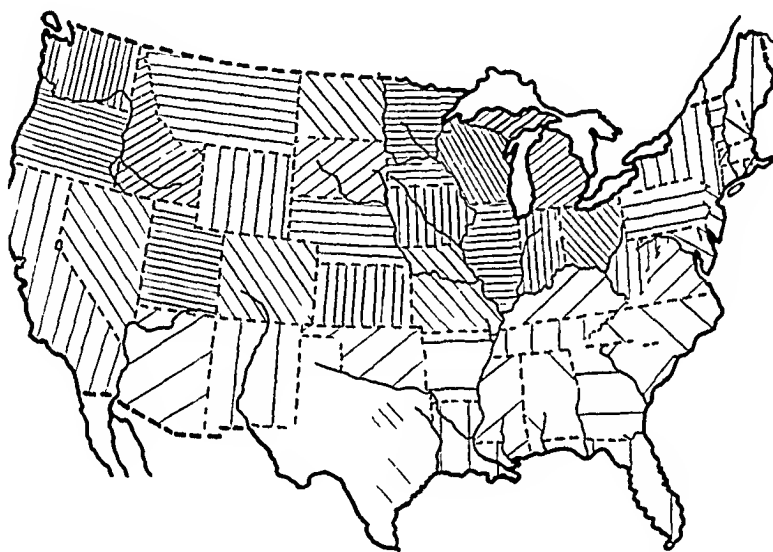


Fig. 3—Mortality from exophthalmic goiter, based on figures published in the United States Mortality Reports from 1920 to 1932, inclusive. Since the state of Texas is not in the registration area, only the data from several registration cities in Texas are shown.

the exophthalmic form to occur where endemic goiter is prevalent, but they do not support the conclusion of McClendon and Hathaway<sup>9</sup> that the two types have a common cause. The occurrence of an appreciable amount of exophthalmic goiter along the whole Atlantic seaboard, as previously reported by Crotti,<sup>14</sup> and throughout the South, regions where goitrous districts are few and small, would indicate that factors other than those which operate to produce simple goiter are operative in the production of exophthalmic goiter.

The records of the United States Veterans' Administration presented an opportunity of testing the reliability of the figure 0.57 per

14 Crotti, A. Thyroid and Thymus, Philadelphia, Lea & Febiger, 1922, p. 245.

cent as the incidence of exophthalmic goiter in persons discharged from hospitals throughout the country. The figures,<sup>15</sup> which were not included in my data for reasons already given, show that the incidence of this disease was 0.39 per cent among 541,430 discharged patients, almost all of whom were men between the ages of 35 and 60 years. I assume that the accuracy of this figure is somewhat greater than the one I report because of greater diagnostic facilities, longer opportunity for observation, uniform nomenclature and other advantages which obtain in the veterans' hospitals. It is to be expected that an incidence of 0.39 per cent among the veterans would be less than the one of 0.57 per cent which I obtained for the whole population, since exophthalmic goiter is known to occur about four times more often in women than in men.

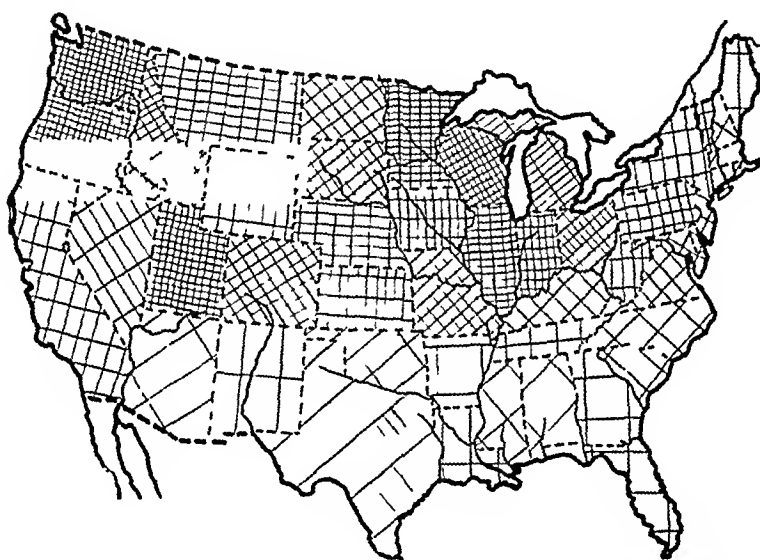


Fig 4—Incidence of exophthalmic goiter in the United States. This is a composite of figures 2 and 3, the cross hatching being produced in the same manner as that in figure 1.

#### HIGH, UNIFORM INCIDENCE IN CITIES

Table 2 shows the incidence of exophthalmic goiter in some of the large cities according to my survey. In every case the average for the cities in an area exceeded the average for the whole geographic area in which they lie. Naturally, large urban communities will attract a certain number of patients because of the hospital facilities for treatment, especially for surgical treatment, which they afford. This may explain the high incidence (of 0.84 per cent) for Boston, where a majority of the patients with toxic goiter in New England are referred. But it does not explain why such widely separated cities as Philadelphia,

<sup>15</sup> Griffith, C. M., Medical Director, Veterans' Administration, Washington. Personal communication to the author.

Chicago, St Louis and Minneapolis should have hospital admission rates of from 0.88 to 0.99 per cent for exophthalmic goiter. Only two of these cities are located in goitrous districts. It is thus seen that when data from large urban communities are compared, exophthalmic goiter is as frequent in the areas where goiter is not endemic as in those where it is endemic.

A greater incidence of thyrotoxicosis in large cities was found by Sallstrom<sup>8</sup> to occur also in Sweden. That this was true even before thyroidectomy in urban hospitals became the treatment of choice is supported by a bit of evidence published in 1878. At the twenty-eighth annual meeting of the Illinois Medical Society, Earl<sup>16</sup> summarized the experience of thirty-six physicians in respect to exophthalmic goiter and it is clear that the incidence was greater in cities.

TABLE 2—*Morbidity from Exophthalmic Goiter in Cities in Which Five or More Hospitals Were Included in Survey*<sup>17</sup>

City	No of Hospitals in Survey	Exophthalmic Goiter, Per centage	City	No of Hospitals in Survey	Exophthalmic Goiter, Per centage
Boston	6	0.84	Chicago	15	0.88
New York	16	0.36	Milwaukee	5	1.42
Brooklyn	7	0.51	Minneapolis	7	0.97
Philadelphia	5	0.90	Mean for North Central cities		0.98
Washington	5	0.47	Pittsburgh	7	0.68
Baltimore	6	0.52	St. Louis	7	0.99
Mean for Atlantic Coast cities		0.72	Los Angeles	6	0.76
			San Francisco	8	0.58

#### COMMENT

The data presented here show that exophthalmic goiter occurs in every part of the United States, although it is encountered more frequently in districts where goiter is endemic. Simple goiter is confined chiefly to the large regions in which goiter is endemic. On the basis of these incidences it appears that the two types of goiter have different causes.

The high and almost uniform occurrence of exophthalmic goiter in large cities indicates that some of its etiologic factors are related to conditions of urban existence. It has been suggested that the nervous strain of modern industrial and commercial civilization is a precipitating factor. Many students of this malady claim that its occurrence is definitely more frequent among civilized peoples. The excitement,

<sup>16</sup> Earl, C. W. Graves' Disease. Its Frequency in Illinois, with a Brief Consideration of Its Recent Pathology and Treatment, Tr. Illinois M. Soc. **28**: 63, 1878.

activity and constant alertness required for survival in the modern civilized world have been named as potent etiologic factors. Exophthalmic goiter is believed to be a disease which may be latent in a person living in a natural or sheltered environment, but which will develop under the stress of anxiety and fear. If this is true it may explain why there is more exophthalmic goiter where there is concentration of population in cities, with a highly competitive struggle for existence which does not vary greatly from city to city.

#### SUMMARY

Statistical studies of the comparative incidences of endemic goiter and exophthalmic goiter in the United States are presented. These show that the latter occurs more uniformly throughout the country, even being present in regions where endemic goiter is unknown, which indicates that the two types of goiter are etiologically unrelated.

# EARLY MANIFESTATIONS OF PRIMARY CARCINOMA OF THE LUNG

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AND

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If cancer of the lung is to be diagnosed at a time when it will still be amenable to some therapeutic measure, it must be diagnosed early. Meakins<sup>1</sup> has defined a case of early cancer of the lung as one in which "the original tumour is still localized and has not as yet involved either the peribronchial and mediastinal glands or any other adjacent structures, and before extensive pulmonary, pleural, or distant metastases have occurred." A neoplasm of the bronchial tree, beginning as an invasion of a relatively small part of the bronchial structure, must first produce irritation, erosion, hemorrhage, pressure, infection or obstruction before gross symptoms referable to the thorax will be elicited. The primary growth in such instances will rarely cause pain in the early stages. "The early diagnosis depends on a careful consideration of what often appear to be trivial symptoms."

At present, when cough seems to be habitual with the average person, every patient with a cough cannot be looked on with suspicion as having neoplasm of the lung. But when the cough habit peculiar to a person changes and is accompanied by tightness in the lower sternal region, wheezing or a change in the character of the breathing, that patient, if he is of "cancer age," should be suspected of having neoplasm of the lung until this condition is definitely ruled out. The solution of the problem of bronchogenic carcinoma in large measure depends on early recognition of the growth. The incidence of carcinoma of the lung is believed to be increasing, but whether the increased number of cases reported in the literature indicates a real increase is still debatable.

It is our object in this communication to present, first, a group of patients with a history of thoracic symptoms of less than one month's duration and, second, a group of patients without thoracic symptoms

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1 Meakins, J C. The Early Diagnosis of Carcinoma of the Lung, *Canad M A J* **30** 283-285, 1934

for whom a final diagnosis of carcinoma of the lung was made. On the basis of these cases the earliest manifestations of the disease will be emphasized.

The material for this paper was taken from the case records of patients admitted to the Jewish Hospital of Brooklyn between 1917 and 1936, inclusive. In this period there were admitted 170 patients with carcinoma of the lung, 47 of whom were free from thoracic symptoms until about one month before admission and another 13 of whom gave no history referable to the thorax. It is the latter group of 60 patients which forms the basis of this study. The patients to be presented fall into three groups:

1 Those patients for whom the diagnosis was made from the history, clinical course and roentgen studies (25 cases)

2 Those for whom the diagnosis was also confirmed by bronchoscopic examination, biopsy (of tissue removed at bronchoscopic examination and of a lymph node), puncture of the lung or the presence of malignant cells in the sputum, in the expectorated tissue or in the pleural fluid (22 cases)

3 Those for whom the diagnosis was further confirmed by necropsy studies (13 cases)

#### ETIOLOGY

Numerous theories have been advanced as to the bearing of inhalation of dusts or of tar from roads as a possible etiologic factor in carcinoma of the lung. No evidence of any such connection has ever been proved. Nor have tuberculosis, influenza, tobacco and war gases been shown to be etiologic agents. Rostowski,<sup>2</sup> in a survey of pulmonary cancer among miners of Schneeberg, in Bavaria, found that in the drilling of the hard rock in these mines, great quantities of dust are produced which is somewhat radioactive and which is composed of minute sharply angled particles. The arsenic content of this dust is 0.45 per cent. Schmorl<sup>3</sup> likewise reported a study of 154 miners of this district for cancer of the lung. He found that in 13 of 21 fatal cases the diagnosis of carcinoma of the lung was substantiated by necropsy. Rostowski stated, "We have never seen a Schneeberg tumor of the lung without an accompanying pneumoconiosis." This does not imply that pneumoconiosis is the cause of the neoplasm. Recently Kennaway and Kennaway<sup>4</sup> have shown that the factors which lead to

2 Rostowski, O. Clinical and Radiological Study of Schneeberg Lung Cancer, in Report of the International Conference on Cancer, Baltimore, William Wood & Company, 1928, p. 269.

3 Schmorl, G. Ueber den Schneeberger Lungenkrebs, Verhandl. d. deutsch. path. Gesellsch. **19** 192-196, 1923.

4 Kennaway, N. M., and Kennaway, E. L. A Study of the Incidence of Cancer of the Lung and Larynx, J. Hyg. **36** 236-267, 1936.

silicosis appear not to be active in the production of cancer of the lung. They also have shown that in certain open air occupations in which there is exposure to the dusts of the road, the percentage of cases of carcinoma of the lung was high, whereas drivers of motorcars had a normal incidence. In this study they also showed that workers exposed to coal gas and tar tend to have a higher incidence of cancer of the lung. Since the publication of Adler's <sup>5</sup> monograph on the subject of carcinoma of the lung (1912), in which he presented 6 cases of post-traumatic carcinoma, considerable controversy has arisen. Weller <sup>6</sup> has emphasized that a single external trauma cannot be held responsible for the development of pulmonary cancer. He stated that Aufrecht concluded that severe trauma which does not produce laceration of the pulmonary tissue but only molecular disturbance of an unknown character is an important immediate cause of pulmonary cancer.

In the cases presented in this paper, no particular occupation or type of work appeared to be concerned. The industries and occupations

*Number and Percentage of Cases*

Age, Yr	Men	Women	Total
21-30	1 (1.7%)	0	1 (1.7%)
31-40	2 (3.3%)	2 (3.3%)	4 (6.7%)
41-50	9 (15.0%)	1 (1.7%)	10 (16.7%)
51-60	19 (31.7%)	5 (8.3%)	24 (40.0%)
61-70	15 (25.0%)	4 (6.7%)	19 (31.7%)
71-75	1 (1.7%)	1 (1.7%)	2 (3.4%)

represented constituted a cross section of the type of work carried on in the community at large.

#### AGE AND SEX INCIDENCE

Like cancer in the other parts of the body, cancer of the lung generally attacks persons over 40 years of age, although a number of cases have been reported in patients between 20 and 30 years of age. It has been encountered in rare instances in patients under 20 years of age. Beardsley <sup>7</sup> has reported on the youngest patient, a child of 16 months, with primary carcinoma of the lung. Arkin and Wagner, <sup>8</sup> in a series

<sup>5</sup> Adler, I. Primary Malignant Growths of the Lungs and Bronchi, New York, Longmans, Green & Co., 1912.

<sup>6</sup> Weller, C. V. The Pathology of Primary Carcinoma of the Lung, Arch Path **7** 478-519 (March) 1929.

<sup>7</sup> Beardsley, J. M. Primary Carcinoma of the Lung in a Child, Canad M A J **29** 257-259, 1933.

<sup>8</sup> Arkin, A., and Wagner, D. H. Primary Carcinoma of the Lung. A Diagnostic Study of One Hundred and Thirty-Five Cases in Four Years, J A M A **106** 587-591 (Feb 22) 1936.

of 135 patients, found that 43.7 per cent were in the 51 to 60 year group and 72 per cent in the 41 to 60 year group

In the present study the youngest patient was a man aged 30 years, and the oldest was a woman aged 75 years. The age-sex incidence in our series of cases is shown in the accompanying table. There were 49 patients between the ages of 45 and 65 years, an incidence during this twenty year span of life of 81.7 per cent. There were only 6 patients between 30 and 43 years of age (an age incidence of 10 per cent) and 5 patients between 66 and 75 years (an age incidence of 8.3 per cent).

All observers seem to agree that the disease occurs more frequently amongst males. Moses,<sup>9</sup> in a study of 287 patients at Kings County Hospital, found 204 males and 83 females, 70 per cent of his series being males. Edwards,<sup>10</sup> in a series of 73 patients, found 53 males, an incidence of 72.6 per cent. In our series there were 47 (78.3 per cent) men and 13 (21.7 per cent) women.

#### SIGNS AND SYMPTOMS

There are no symptoms pathognomonic of carcinoma of the lung. It is a common mistaken belief that the disease always causes symptoms referable to the thorax. Thirteen (21.7 per cent) of the patients included in this study gave no history of symptoms referable to the chest. Arkin and Wagner, in a comprehensive study of 135 cases of pulmonary carcinoma, noted that in 51 per cent of the patients the signs and symptoms were predominantly outside the lungs and that in only 49 per cent were the symptoms largely thoracic. Rogers,<sup>11</sup> in a survey of 50 patients, found that 44 per cent gave as their first symptom one that was not connected with the chest and that 12 per cent went through the entire course of illness without pulmonary symptoms. Jaffé,<sup>12</sup> in a review of 100 patients with carcinoma of the lung coming to autopsy observed that 24 (24 per cent) gave no history of symptoms pointing to an intrathoracic lesion. Of equally great importance is the fact that the character of the onset is so variable. The onset may be insidious, simulating that of prolonged bronchitis or gastric disturbance, or it may be acute, simulating an acute pneumonic process. The disease not infrequently is chronic and progressive, with epigastric distress,

9 Moses, H. M. Cancer of the Lungs, *M. Times*, New York **64** 477, 1936.

10 Edwards, A. T. Malignant Disease of the Lungs, *J. Thoracic Surg.* **4** 107-124, 1934.

11 Rogers, W. L. Primary Cancer of the Lung. A Clinical and Pathologic Survey of Fifty Cases, *Arch. Int. Med.* **49** 1058-1077 (June) 1932.

12 Jaffé, R. H. The Primary Carcinoma of the Lung. A Review of One Hundred Autopsies, *J. Lab. & Clin. Med.* **20** 1227-1237, 1935.



nausea, constipation and other symptoms. Formerly it was believed that such symptoms appeared late and were the result of metastasis. While they do occur in the late stages, they are not necessarily the result of spread of the neoplastic process. The local irritative process of a foreign body (the neoplasm) may cause an irritative cough, episodes of infection within the lung may cause repeated attacks of "pneumonia" or as a result of local pressure on a nerve (vagus or phrenic) in the region of the hilus, there may be symptoms which are manifestly intra-abdominal. These symptoms may appear jointly or independent of each other and may therefore be misleading as to the site of origin. It is particularly the patient with the latter group of symptoms who is neglected. The clinician who investigates a patient for an intra-abdominal pathologic condition and fails to find any or not enough evidence to be commensurate with the complaints should not neglect to examine the thorax carefully.

Of the 47 patients in whom thoracic symptoms were present on entry, cough was present in 43 (91.5 per cent), pain in the chest, in 27 (57.7 per cent), expectoration, in 21 (44.7 per cent), dyspnea, in 20 (42.5 per cent), loss of weight, in 20 (42.5 per cent), hemoptysis and/or blood-streaked sputum, in 19 (40.4 per cent), asthmatic wheezing, in 16 (34 per cent), malaise in 14 (29.8 per cent), epigastric distress and substernal discomfort, in 13 (26.8 per cent), anorexia, in 13 (26.8 per cent), a temperature above 100.5 F, in 9 (19.1 per cent), night sweats, in 9 (19.1 per cent), hoarseness, in 7 (14.8 per cent), pain in the neck, shoulder and/or arm, in 7 (14.8 per cent), pain in the sacroiliac region, in 6 (12.7 per cent), and nausea and vomiting in 4 (8.5 per cent).

In the 13 cases in which there were no thoracic symptoms the most frequent complaints were, in the order of their frequency, as follows: epigastric distress in 7 (53.9 per cent), anorexia in 7 (53.9 per cent), nausea and vomiting in 6 (46.2 per cent), malaise in 5 (38.5 per cent), loss of weight in 4 (30.8 per cent), constipation in 4 (30.8 per cent) and aphasia in 2 (15.4 per cent). These symptoms were progressive and did not yield to the usual symptomatic therapy. The cause of these abdominal complaints and symptoms could not be explained on the basis of an abdominal investigation. Epigastric distress sooner or later became manifest in 10 (77 per cent) of the patients. This was particularly true when the left side was involved and when the primary neoplastic focus was basal. In this group of patients the duration of the symptoms before the diagnosis was made varied from three weeks to five years, and in every instance the patient sought medical advice before admission to the hospital. In more than half the cases the patient was treated, without relief, for over a year for a supposedly obscure intra-abdominal condition.

A statistical analysis of the symptoms which the patient showed when admitted to the hospital is, in our opinion, not as satisfactory as the general impression gained from an analysis of the train of symptoms which each patient had had up to the time of admission to the hospital. One fact stands out boldly—the general well-being of each patient, in spite of his condition and complaints. The character of the onset is of the utmost importance. In some instances the symptoms were ushered in insidiously with a protracted cough, tightness in the lower portion of the chest, expectoration and wheezing—all of which failed to respond to symptomatic therapy. In the occasional case there was relief for a short time, after which all the symptoms recurred and were accompanied by various degrees of constant pain in the chest, malaise and loss of weight. In other instances the symptoms were ushered in acutely, with chills, fever, cough and expectoration lasting for several days, leaving the patient prostrated and unable to recover his former virility. Frequently the cough would become more disturbing, the weakness progressive and the expectoration bloody, or the patient would have frank hemoptysis. The textbook sign of “currant jelly sputum” in carcinoma of the lung was the exception rather than the rule. Not infrequently the patient would point to the midsternal region and complain of “something there” which would not allow him to take a deep breath. In addition to these findings, the clinical picture often tended to be confused by the fact that the patient complained of epigastric distress, nausea, vomiting after meals, headache, constipation, aphasia, swelling of the ankles and dysuria. Or the latter train of symptoms would develop without any symptoms referable to the thorax. In the 13 cases in which there were no thoracic symptoms, the first symptoms which brought the patient to the physician for medical aid were anorexia, epigastric distress, nausea and vomiting, malaise, loss of weight, constipation, aphasia, edema of the ankles, pruritis, prolapsed hemorrhoids and jaundice. In these cases, because of the resistance to symptomatic treatment and the progressive weakness with ill defined paroxysmal dyspnea or prolonged symptoms referable to the upper portion of the abdomen, a routine roentgen examination of the thorax gave the first clue to the unexpected diagnosis of carcinoma of the lung.

In this series of 60 cases there were 13 instances of neoplasm of the bronchus of the lower lobe in which epigastric distress was most disturbing to the patient and was his chief complaint on admission to the hospital. In 9 of these cases the lesion was on the left side, whereas in only 4 cases was it on the right side. When it was on the left side, the complaints referable to the upper portion of the abdomen appeared more severe, came on earlier and were of longer duration than when the neoplasm was on the right side.

## PULMONARY SIGNS

In the early stages the physical findings are extremely variable, ranging from none to a few indefinite signs, which vary further with the location and the size of the primary growth. In this connection three locations must be recognized: (1) hilar, (2) parenchymal and (3) peripheral. The hilar location in the early stages may cause some unilateral impairment, noted on percussion posteriorly in the region between the fifth and the eighth dorsal vertebra. This, however, is difficult to elicit, especially on the left side. The breath sounds in this region may have a tubular, asthmatoïd character, owing to partial obstruction of the bronchus or retention of bronchial secretions. In the lobe supplied by the bronchus containing the growth there may be heard a prolonged expiratory sound, occasionally accompanied by fine crackling rales. In the parenchymal type, percussion may show no changes, because of the surrounding normal or emphysematous lung. The breath sounds, however, are somewhat suppressed in the area of the growth and may have a distant tubular quality. In the peripheral type there is usually impairment of percussion at the site of the growth, with somewhat distant breath sounds. Since in these cases fluid frequently develops, signs of an encapsulated hydrothorax may be elicited.

However, in a number of cases no signs are elicited in the early stages, but from the history and clinical course one is led to believe that a neoplasm may be present. Such a case must be investigated further to prove or rule out the presence of a neoplasm. The persistence of an area of impaired percussion with depressed breath sounds or cornage, in the absence of recent infection of the respiratory tract, should be considered as due to carcinoma until proved otherwise. The signs and symptoms are generally not sufficient to warrant a definite diagnosis of the disease but only indicate the possibility of its presence. It is then necessary for the clinician to persist in his investigation of the case until a final diagnosis is reached. Granted that the findings of a careful physical examination of the chest by an experienced clinician may lead to the suspicion of a carcinoma of the bronchus, the diagnosis cannot be made without such accessory methods as roentgenographic examination, bronchoscopic examination and microscopic examination of representative tissue removed at the time of the bronchoscopic examination.

Roentgen examination at an early stage will show minimal changes. In fact, in the earliest stages there are no appreciable roentgenographic changes. In cases in which the growth is still local and early, the changes vary with the location of the neoplasm. In the hilar type there may be unilateral opacity in the region between the fifth and the eighth dorsal vertebra which is either crescentic, with its convexity toward the lung on the side of the neoplasm, or triangular, with the base toward that

side Occasionally some reactionary pneumonitis is also seen about the opacity In the parenchymal type there is a distinct ovoid or spherical area in the pulmonary tissue with a relatively even border At times strands of infiltrated tissue lead from the growth Carman<sup>13</sup> said he believed this to be pathognomonic of carcinoma of the lung In the peripheral type there is a solitary opacity, usually in the axillary region, which is triangular, with the apex pointing into the pulmonary tissue Since in these cases fluid develops relatively early, localized hydrothorax may also be present and may partly obscure the primary growth When the diagnosis is uncertain the fluid should be removed, and then a roentgen examination should be made At the same time a small pneumothorax may be induced which will act as a contrast medium and will also replace the opacity of the fluid

A single anteroposterior or posteroanterior roentgenographic study is valueless in the demonstration of the presence of an early neoplasm Oblique and lateral roentgenograms must also be made so as to permit visualization of the pulmonary field from every possible angle Many roentgenologists believe that stereoscopic roentgen studies are the only means whereby one can locate early carcinoma of the lung

As an adjuvant to any of these methods of roentgen study, bronchographic examination is frequently of aid in locating the site of the lesion Such studies reveal a relatively small growth as a filling defect in the bronchial wall or as partial bronchostenosis, owing to the encroachment of the growth on the lumen of the bronchus

Bronchoscopic study and biopsy of tissue removed bronchoscopically are of the utmost importance in the early diagnosis of carcinoma of the lung and constitute the greatest aid available at present for the early establishment of the diagnosis A competent bronchoscopist can directly inspect and remove for pathologic studies a small growth which is producing minimal symptoms and no roentgen changes Bronchoscopic examination may lead to the suspicion of a malignant growth, but the final diagnosis rests on the pathologic study of the tissue removed at the time of the bronchoscopic examination Jackson and Konzelmann,<sup>14</sup> in an excellent study on the bronchoscopic observations in carcinoma of the lung, stated that they had been able to make the diagnosis in over 75 per cent of their cases They also added

Many of the cases in which biopsy is not possible at the first bronchoscopy will later show endobronchial intrusion, though the surgeon should not wait for this if consent is given for exploratory thoracotomy Even in cases where biopsy

13 Carman, R. D. Primary Cancer of the Lung from the Roentgenologic Viewpoint, *M. Clin. North America* 5 307-355, 1921

14 Jackson, C. L., and Konzelmann, F. W. Bronchial Carcinoma. Bronchoscopic Biopsy in a Series of Thirty-Two Cases, *J. Thoracic Surg.* 4:165-186, 1934

is *not* possible, bronchoscopic findings may be of definite diagnostic value. Microscopic evidence of malignancy does not imply necessarily an extensive infiltrative tumor, and therefore the grading of bronchogenic carcinomas should be tempered by a knowledge of the bronchoscopic and roentgenographic findings. Biopsy studies are of great value, yet constitute but one of the important considerations in the diagnosis of bronchogenic tumors. Teamwork by the bronchoscopist, radiologist, and pathologist will accomplish a proper prognosis and guide the patient to the most beneficial form of treatment.

An indefinite history, a few abnormal physical findings and a suspicious roentgenogram are not sufficient evidence on which to condemn a patient as having carcinoma of the lung. They are, however, sufficient muniments to necessitate the clinician's further investigation of the case until he has established a satisfactory diagnosis. In the differential diagnosis the following conditions must be considered: abscess of the lung, actinomycosis of the lung, aortic aneurysm, atelectasis, benign tumor of the lung, bronchiectasis, bronchitis (chronic), cardiovascular disease, tumor of the thoracic wall, congenital cystic disease of the lung, echinococcus cyst of the lung, endothelioma of the pleura, a foreign body in the bronchus, Hodgkin's disease, infarct (pulmonary), interlobar effusion, lymphosarcoma (mediastinal), metastatic tumor of the lung, esophageal tumor, pericardial effusion, pneumoconiosis, pneumonia (bronchopneumonia and lobar pneumonia), pleural effusion, sarcoma of the lung, tumor of the superior sulcus, syphilis of the lung, thymoma, intrathoracic thyroid gland, tuberculosis of the lung, varices and vicarious menstruation.

#### REPORT OF CASES

A group of exemplary cases is presented in each of which there were unusual clinical features or in which a diagnostic problem existed the solution of which was obtained by some accessory procedure and in some instances was further confirmed by necropsy.

Cases 1 and 2 show the importance of bronchoscopic study and biopsy of tissue removed at bronchoscopic examination in the early recognition of bronchogenic carcinoma.

**CASE 1**—M. H., aged 59 years, a trader, was admitted to the hospital on June 13, 1932, because of cough and expectoration for three weeks. He had been in good health up to the time of the present illness except for an infection of the upper respiratory tract nine months prior to the present illness. During that illness he had a nonproductive cough which lasted approximately three weeks and which on one occasion was accompanied by blood-tinged sputum. Three weeks prior to entry he had a "cold," which was relieved by symptomatic medication. The cough, however, did not entirely disappear, and two days before entry it suddenly became paroxysmal and was accompanied by bloody expectoration. At this time the patient began to experience more or less constant substernal discomfort and a sensation of pressure along the anterior costal margins. The temperature ranged between 99 and 100.5 F. There had been a loss of 3 pounds (1.3 Kg.) in the past three weeks.

The patient was well developed, he was slightly cyanotic about the lips and appeared fatigued. The chest was emphysematous and moved poorly with respiration. There was impairment to percussion at the base of the left lung posteriorly, the remainder of the pulmonary fields were hyperresonant. The breath sounds at the base of the left lung were distant and bronchovesicular and were accompanied by fine moist rales. The other systems were essentially normal. Study of the blood showed 11,600 white cells, with 70 per cent polymorphonuclears, 26 per cent lymphocytes and 4 per cent mononuclears. The hemoglobin value was 76 per cent, and the red blood cells totaled 4,000,000. Roentgenographic examination of the chest showed bilateral infiltration of the hilus, with extension in the direction of the base. There was no evidence of a localized pathologic pulmonary lesion.

The patient was discharged on June 22, with a diagnosis of chronic bronchitis. One month later, because of the persistence of the symptoms, he was readmitted. The physical findings, laboratory studies and roentgen examinations of the chest were essentially the same as at the previous admission. This time the patient was subjected to bronchoscopic examination. The right main bronchus was normal. In the left main bronchus there was a bilobed polypoid mass which extended into the upper part of the bronchus. The impression was gained that this growth was a malignant neoplasm. A specimen was taken for biopsy. The pathologist reported that the tissue showed papillary adenocarcinoma of the bronchus.

*Comment*—A patient of "cancer age," in whom there suddenly develops a persistent cough, whether accompanied by bloody expectoration or not, may have chronic bronchitis the etiology of which must be considered to be carcinoma of the bronchus until proved otherwise. This case shows the importance of bronchoscopic examination and biopsy of tissue removed bronchoscopically as further aids in establishing a diagnosis.

CASE 2—E. A., a woman aged 66 years, was admitted to the hospital on Jan. 2, 1933, complaining of pain in the upper portion of the abdomen, painful cough and expectoration of six days' duration. Two weeks prior to entry she began to cough, without apparent reason. The cough was hacking and unproductive. It continued until six days before entry, when she began to have persistent sharp pains across the upper portion of the abdomen. The pains radiated along the lower ribs to both posterior infracostal regions. At the same time the cough became productive, and she raised some blood-streaked sputum, the temperature became elevated, and she experienced marked dyspnea on exertion.

Examination on entry revealed an obese woman with cyanotic lips and finger tips. She was obviously in distress and breathed rapidly. The thorax was symmetric, the left side lagging during respiration. There was tenderness in the lower costal region on the left side posteriorly. Both bases were impaired to percussion, but much more so on the left. The breath sounds were tubular at the base of the left lung and bronchovesicular throughout the remainder of the pulmonary fields. There were no adventitious sounds. The remainder of the physical examination revealed essentially no abnormality. A blood count showed 11,700 white cells, with 80 per cent polymorphonuclears, 12 per cent lymphocytes and 8 per cent mononuclears. The hemoglobin value was 65 per cent, and the red blood cells totaled 3,300,000. Except for a slightly elevated sugar content, chemical study of the blood gave essentially normal values. Roentgenographic examination of the chest showed bilateral basilar infiltration extending toward

the hilar regions. The infiltration was more pronounced on the left side. The left costophrenic sinus was obliterated by a small amount of fluid.

Several days after entry, some of the pleural effusion on the left side was aspirated. It was turbid and yellowish, and cytologic examination revealed many red blood cells and lymphocytes. There were many greatly enlarged cells with hyperchromatic nuclei which showed characteristics usually associated with cells of malignant origin. The patient's temperature for the first five days of hospitalization ranged between 100 and 103 F and then fell by lysis to about 100 F. She was discharged after thirty-five days of hospitalization, with a diagnosis of bronchopneumonia. There was still considerable infiltration at the base of the left lung, and there was glandular enlargement at the left hilus.

The patient was readmitted to the hospital one month after discharge. Five days prior to that entry the cough and expectoration, which were persistent, suddenly became worse and were accompanied by bouts of elevation in temperature. The sputum was once more blood tinged. Physical examination showed the right lung to be clear. The left lung was impaired to percussion throughout, with no breath sounds. Roentgenographic examination showed the left side of the chest to be homogeneously opaque. The mediastinum was not displaced. The roentgenologist commented, "I am inclined to believe that there is considerable fluid present. Whether or not there is compression atelectasis of the lung, I hesitate to state, but it is worthy of note that the heart is apparently on the affected side. This condition is not at all uncommon with neoplastic disease primarily in the bronchus." A bronchographic study showed definite blockage of the left main bronchus just below the level of the carina, preventing the entrance of any iodized poppyseed oil 40 per cent into the lung or bronchus distal to the obstruction. Some of the pleural effusion was removed. It was serohemorrhagic and did not present any of the characteristics of a malignant growth. Bronchoscopic examination revealed that the carina and the orifice to the right main bronchus were apparently normal. The entrance to the left main bronchus was obstructed by a thick purulent secretion. After aspiration of this material the bronchus was seen to be completely obstructed by a grayish tumor of somewhat glistening appearance. The mass could not be removed. The impression was gained that this was an intrabronchial tumor (of the left main bronchus) which was probably malignant. A biopsy specimen was taken. Microscopic examination of the tissue showed degenerated epithelial cells growing in a disorderly manner characteristic of carcinoma.

*Comment*—This case is of interest, first because it shows the paucity of physical findings and roentgenographic changes which attend early carcinoma of the lung. Second, it points out that a patient of "cancer age" in whom there develops an infection of the bronchial tree which assumes an unusual course may have underlying carcinoma. It is of additional interest because the accessory methods available for the diagnosis were not employed at the first admission to the hospital, at which time the pleural effusion suggested carcinoma of the lung. This is another instance in which the ultimate diagnosis depended on bronchoscopic study and on microscopic study of tissue removed at the time of the bronchoscopic examination.

Cases 3 and 4 show that when biopsy of tissue removed bronchoscopically reveals no abnormality, bronchogenic carcinoma is not ruled out.

CASE 3—E J, aged 64 years, a painter, was admitted on Sept 30, 1934 with a history of cough for five weeks and dyspnea for three weeks Six weeks before entry a sense of pressure developed in the lower part of the chest without apparent cause One week later he began to cough, and the cough steadily increased in severity Three weeks before entry he noticed that he was becoming dyspneic on even slight exertion There was no history of expectoration, hemoptysis or loss of weight

Examination showed a fairly well developed man who was acutely ill The trachea was deviated to the right The chest was symmetric, with decreased respiratory excursions on the left side The right lung was essentially normal to percussion and auscultation The left side of the chest was flat to percussion, and the breath sounds were not audible The mediastinum was not displaced There were a few small lymph nodes on the left side of the neck A blood count showed 8,400 white cells, with 81 per cent polymorphonuclears, 13 per cent lymphocytes, 5 per cent mononuclears and 1 per cent eosinophils The hemoglobin value was 78 per cent and the red blood cell count 4,270,000 • The sedimentation rate was 30 mm in one hour Roentgenographic examination of the chest at the time of entry showed opacity of the left hemithorax without displacement of the mediastinum Bronchographic examination showed an obstruction to the iodized oil at the left main bronchus The pleural fluid within the left hemithorax was removed but reaccumulated within three days Cytologic examination of the pleural fluid on several occasions showed a moderate number of lymphocytes and red blood cells There were also an unusually large number of degenerated epithelial cells, an occasional plaque of degenerated large cells and an occasional signet ring cell The appearance of the fluid was highly suggestive of a malignant condition Bronchoscopic examination showed that about  $\frac{3}{4}$  inch (19 cm) below the entrance to the left main bronchus there was a large, irregular nodular mass attached to the superior wall The mass extended about  $\frac{1}{2}$  inch (13 cm) into the bronchus, at which point it occupied the entire lumen An attempt was made to obtain some of the tissue for microscopic examination, but because of the density of the mass it was difficult to obtain a representative specimen The impression gained at the time of the bronchoscopic examination was that the neoplasm was malignant Microscopic examination of the tissue removed failed to show malignant growth

*Comment*—While the ultimate diagnosis of carcinoma of the lung rests with the observation of malignant cells in the tissue removed from the bronchus, it is not possible in every instance to observe such cells This is due to the fact that the tissue removed is not representative of the tumor In this case biopsy of tissue removed bronchoscopically did not suggest malignant growth However, the bronchoscopic observations and the cytologic examination of the pleural fluid did suggest malignant growth This case also points out that if any one examination shows a normal condition, this does not rule out the presence of malignant growth, whereas one positive finding clinches the diagnosis

CASE 4—S N, a man aged 63 years, a clerk, was admitted on Dec 12, 1934, complaining of cough and expectoration of one day's duration Two years previously he had had pleurisy on the left side which lasted approximately two weeks Previous to this he had had a chronic cough with expectoration for about twenty-five years The onset of the present illness began twenty-four hours before entry, at which time he began to feel tightness in the left side of



the chest and in the substernal region. This was accompanied by paroxysms of coughing, with purulent expectoration, the sputum was blood streaked on several occasions. About three months previous to entry the patient had a similar episode, and the condition was diagnosed as abscess of the lung of unknown etiology.

Examination at this time showed a fairly well developed, poorly nourished, acutely ill man. His chest was emphysematous, the sternum was prominent and the interspaces on the left side were wider than those on the right. There was diminished resonance at both bases, more marked on the left side, tactile fremitus was diminished on the left side. The breath sounds were harsh and exaggerated throughout except at the base of the left lung, where they were distant and almost entirely lost in the various-sized moist rales. A blood count showed 9,400 white cells, with 81 per cent polymorphonuclears, 15 per cent lymphocytes and 4 per cent mononuclears. There were 4,260,000 red blood cells. The hemoglobin value was 50 per cent. A roentgenographic examination of the chest showed a dense opacity involving the periphery of the left lung, with infiltrating bands leading toward the hilus and base on that side. Bronchographic examination outlined a normal bronchial tree on the right side. On the left side the iodized oil did not extend beyond the main bronchus. In the pulmonary tissue distal to the obstruction there was a large globular opacity with a clear superior zone and a horizontal fluid level inferiorly. These findings suggested a large pulmonary abscess with a fluid level. Bronchoscopic examination was performed, and a diagnosis of abscess of the lung was made. The findings did not suggest a malignant growth. A microscopic examination of the tissue removed at the time of the bronchoscopic examination showed no evidence of malignant growth. The patient was treated for abscess, and surgical drainage was instituted. He died shortly thereafter. At necropsy, a cavitated carcinoma of the upper lobe of the left lung was present.

*Comment*—In this case there was carcinoma of the lung with excavation which presented all the appearances of an abscess. The accessory methods of diagnosis available were of no help. In retrospect and on reexamination of the roentgenograms we noted that the cavity was of unusual thickness and irregularity. This is not characteristic of a pulmonary abscess of so short a duration. Such findings are more commonly seen in the highly undifferentiated types of carcinoma of the lung.

Cases 5 to 9 illustrate the importance of cytologic examination of the pleural fluid and microscopic examination of a lymph node or nodule of the skin.

CASE 5—A S., a woman aged 68 years, was admitted on July 29, 1930, complaining of weakness, cough, blood-streaked sputum and dizziness for about one month. She had been perfectly well until the onset of the present illness. She went to bed one night feeling as well as usual and awoke the following morning with a cough, without apparent cause. After this episode she continued to expectorate "little lumps which contained blood." The cough became more persistent and troublesome. Two weeks prior to entry she began to notice progressive weakness and excessive night sweats, she became dizzy on getting out of bed and therefore remained confined to bed. She had lost about 20 pounds (9.1 Kg.) since the onset of the illness.

The patient appeared to be chronically sick. She was cyanotic about the lips and showed evidence of recent loss of weight. The thorax was symmetric and

moved fairly well on respiration. There was dullness to percussion at the base of the right lung, in which area the breath sounds were distant and were accompanied by fine moist rales. The mediastinum was not displaced. The remainder of the physical examination revealed essentially no abnormality. A blood count showed 6,200 white cells, with 64 per cent polymorphonuclears, 28 per cent lymphocytes, 6 per cent mononuclears and 2 per cent eosinophils. The hemoglobin value was 80 per cent, and the red blood cells totaled 4,200,000. Roentgenographic examination of the thorax at the time of entry showed an infiltration of both hilar regions, which was more pronounced on the right side. On this side there was also an infiltrative process extending from the hilus toward the base. Two weeks later, reexamination of the thorax roentgenographically showed an opacity at the base of the right lung, with a clearcut upper linear border delineating the upper border of the lower lobe. The opacity obliterated the diaphragmatic cusp and the costophrenic sinus.

Bronchoscopic study showed that the bronchus of the lower lobe of the right lung contained a smooth papular growth. The impression was gained that this growth was malignant. (No biopsy specimen was obtained.) A small nodule which developed in the skin was removed for microscopic examination. The tissue was diagnosed as "metastatic carcinoma." In the interim a pleural effusion had developed on the right side. Some of this was removed for cytologic examination and suggested the presence of malignant growth. The patient died on September 4. At necropsy, carcinoma of the right main bronchus was present.

*Comment*—This case illustrates the confirmative diagnostic information which may be obtained by early bronchoscopic examination, cytologic examination of the pleural effusion or biopsy of an accessible nodule.

CASE 6—Z. K., aged 65 years, a clothing presser, was admitted on April 1, 1936, complaining of dyspnea, cough, headache and substernal pressure for about five weeks. For the past three months he had been feeling "out of sorts." However, no definite complaints were made until five weeks before entry, when he noted that he was becoming dyspneic while engaged in his usual work. At about the same time he also noted that he had a cough which was becoming troublesome and persistent. In the two weeks before entry the cough had been hacking and had been accompanied by a small amount of expectoration. One week before entry the patient began to have substernal discomfort, headaches and dizziness.

Examination showed a well preserved man, who was somewhat cyanotic about the lips and finger nails. The chest was emphysematous, the left side failed to move as well as the right side during respiration. The intercostal spaces on the left side appeared narrowed. The right side of the chest was essentially normal to percussion and auscultation. The left side was flat to percussion, and the breath sounds were distant and accompanied by numerous fine moist rales. The adventitious sounds were most pronounced at the base posteriorly. The mediastinum was not displaced. A blood count showed 8,700 white cells, with 59 per cent polymorphonuclears, 37 per cent lymphocytes, 2 per cent mononuclears, 1 per cent eosinophils and 1 per cent basophils. The hemoglobin value was 78 per cent, and the red blood cells totaled 4,050,000. A roentgenogram showed a homogeneous opacity involving the entire left side of the chest, with a clear apical region. The mediastinum appeared normal. After removal of the pleural effusion the roentgenogram revealed a discrete node in the basal portion of the left lung. (Subsequent roentgenograms showed rapid reaccumulation of fluid.)

Cytologic examination of the fluid showed many erythrocytes and a moderate number of large mononuclear cells with basophilic or clear protoplasm. Some of the nuclei were hyperchromatic and occupied eccentric positions. A few signet ring cells were present. The impression was gained that this fluid was of malignant origin.

*Comment*—The pleural effusion had masked the underlying pathologic condition, and it was not until the fluid had been removed that satisfactory roentgenograms of the underlying lung could be made. This procedure also permitted cytologic examination of the fluid. The rapid reaccumulation of pleural effusion is commonly met with in some forms of carcinoma of the lung.

CASE 7—S O, aged 56 years, a clothing operator, was admitted on Dec 10, 1936, with a history of pain in the chest, cough, a choking sensation for about five weeks and blood-tinged sputum for five days. Several weeks before entry into the hospital he began to have choking sensations which were followed by cough and pain in the chest. This condition persisted and steadily increased in severity. About three weeks before entry the patient began to expectorate small amounts of yellowish sputum, to lose weight and to sweat at night. Despite the increasing severity of the symptoms, he carried on his daily routine until about two weeks before entry. At this time he became so weak that he had to remain confined to bed. About one week before admission to the hospital he began to have blood-streaked sputum and pain in the lower part of the chest, and on one occasion, several days before entry, he had frank hemoptysis.

Examination at the time of entry revealed an acutely sick patient, who was dyspneic while in the recumbent position. The lips and finger tips were cyanosed. Many various-sized cervical glands were palpable. The left side of the thorax appeared retracted and motionless during respiration. There was dulness to percussion over the lower half of the left side of the chest, in which area the breath sounds were absent. The right side of the chest was normal. The heart and mediastinum were not displaced. The blood count showed 12,800 white cells, with 86 per cent polymorphonuclears, 13 per cent lymphocytes and 1 per cent mononuclears. The hemoglobin value was 90 per cent, and the red blood cell count was 5,000,000. The roentgenogram made at the time of entry showed a pronounced haze at the root of the left lung which gradually extended into the pulmonary parenchyma. The diaphragm on that side was elevated, and the lung appeared smaller than the one on the right. The latter showed evidence of bronchopneumonic infiltration.

Bronchoscopic examination revealed that the posterior tracheal wall above the carina contained a small denuded area and ulceration which bled with manipulation. The diagnosis was questionable. No biopsy specimen could be taken. A cervical lymph node was removed, and microscopic examination showed carcinoma simplex (metastatic). The patient died on Jan 3, 1937. At necropsy there was an infiltrating carcinoma in the left main bronchus.

*Comment*—In this case the course and findings were more or less typical of carcinoma of the lung. The neoplasm undoubtedly was present for a considerable time before it produced any interference with function or symptoms.

CASE 8—P P, aged 54 years, a tinsmith, was admitted on July 13, 1932, complaining of pains in both legs and in the lower dorsal region and constipation for several weeks. For the past nine years the patient had been having pain in the lower portion of the back which was most disturbing during prolonged standing or bending. Occasionally the pain would radiate down the thighs. About four weeks before entry it suddenly became more severe and seemed to begin higher up (in the lower portion of the dorsal region). The pain entirely incapacitated the patient. Occasionally he also had short sharp pains in the right infracostal region and constipation.

On examination the patient appeared acutely sick and was obviously in pain. The chest was emphysematous and moved equally on respiration. There was no impairment to percussion, the breath sounds were bronchovesicular throughout and at both bases were accompanied by fine moist rales. There was some tenderness along the lower lumbar portion of the spine. The remainder of the physical examination revealed essentially no abnormality. The blood count showed 14,100 white cells, with a differential count of 80 per cent polymorphonuclears and 20 per cent lymphocytes. Roentgen examination of the lumbosacral region showed some osteoarthritis. On July 27 the patient was discharged, with a diagnosis of osteoarthritis of the lumbosacral region. Six weeks later he was readmitted to the hospital with similar symptoms. This time, however, they were more severe. The physical findings were essentially the same as on the previous occasion except that this time there were some fine rales throughout the right lung and two small nodules in the skin on the anterior abdominal wall. An investigation was instituted to determine the cause of the persistent moist rales in the right lung. A roentgenographic study showed a homogeneous opacity of the upper half of the pulmonary field without cardiac displacement. Bronchographic examination revealed that the lower portion of the bronchial tree was normal. Although special effort was made to visualize the upper lobe, no iodized oil entered beyond the beginning of the bronchus. Biopsy of a cutaneous nodule failed to show any malignant changes. A second biopsy of the skin showed bands of connective tissue lined with cuboidal epithelium. The spaces between the bands contained similar cells. The papillary structure resembled the "type of growth seen with metastasis to the skin from a bronchial carcinoma." On September 16 the patient died. At necropsy there was carcinoma of the main bronchus of the right lung which extended into the upper lobe.

*Comment*—When a patient of "cancer age" shows unexplained pulmonary signs, whether associated with symptoms or not, a pulmonary malignant growth should be suspected. This case is of further interest in that throughout his illness the patient never presented symptoms referable to the respiratory tract.

CASE 9—J Z, aged 62 years, a contract builder, was admitted on Sept 12, 1934, complaining of pains in the chest, face and head for two weeks. About six weeks prior to the present illness he had some pain in the right infracostal region, which he was told was myalgia, he was advised to apply heat locally. In spite of persistent care, the condition became worse. Three weeks before entry he began to have pain along the left side of the face. The next week he noted that the pain was extending upward on the face and was accompanied by a headache on the left side. The pain had also spread downward to the upper part of the left side of the chest. There was no history of cough, expectoration, loss of weight or dyspnea.

The patient appeared comfortable. Some enlargement of the cervical glands was noted on the right, together with tenderness in the right axillary region. The chest was emphysematous, the breath sounds were exaggerated at the base of the right lung. No adventitious sounds were heard. The other systems on physical examination were essentially normal. A blood study showed 7,500 white cells, with 71 per cent polymorphonuclears, 25 per cent lymphocytes and 4 per cent mononuclears. The hemoglobin value was 75 per cent and the total red blood cell count 4,000,000. A roentgenogram showed a flattened, opaque area of density in the right axillary region, with definite erosion of the fourth rib, extending from the posterior to the anterior axillary line. The findings suggested tumefaction in the region of the fourth rib. On the contralateral side there was another nodule toward the periphery of the pulmonary field.

A small amount of the pleural effusion on the right side was removed for cytologic study. Microscopically it consisted of red blood cells and other cells arranged either in groups as individual cells or in the form of plaques. These cells presented the characteristics of a malignant growth.

*Comment*—This patient originally complained of infracostal pain on the right, but this symptom was lost sight of when he began to complain of pain about the left side of the face, head and upper portion of the thorax. The latter symptoms were undoubtedly due to metastatic involvement.

Case 10 demonstrates the importance of careful examination of the material obtained by bronchoscopic aspiration when biopsy of representative tissue is not possible.

CASE 10—W. K., aged 57, a clothing presser, was admitted on March 20, 1936, with a history of cough, pain in the chest, fever and chills for six days. Except for a slight cough for about forty years, the patient had always felt well up to the time of the present illness. The onset of the illness was sudden. His chronic cough was not altered appreciably, nor was it accompanied by any expectoration.

The patient was of slight build. The chest was symmetric, the right side moving less than the left. The percussion note was impaired in the upper half of the right side of the chest. The breath sounds in this region were distant and bronchial and accompanied by fine moist rales. Results of the rest of the physical examination was essentially unimportant. A blood study showed 14,000 white cells, with 80 per cent polymorphonuclears, 16 per cent lymphocytes and 4 per cent mononuclears. The hemoglobin value was 80 per cent, and the red blood cell count was 4,500,000. A roentgenogram taken at the time of entry showed an opacity of the upper two thirds of the right pulmonary field suggestive of consolidation. The temperature during the first three days of the patient's stay in the hospital was irregularly elevated. On April 10 he was discharged, with a diagnosis of pneumonia in the upper lobe of the right lung.

On November 3 the patient was readmitted to the hospital with the same complaints, in addition, he complained of intermittent pains in the right scapular region. In the interim since his discharge he had expectorated blood on several occasions. A roentgenogram taken on this entry showed an opacity occupying the upper lobe of the right lung, including the apex. The diaphragm was elevated, and the trachea deviated to the right. Passive bronchographic examination revealed normal terminal bronchial markings in the base of the right lung. An attempt was made to pass some of the iodized oil into the region of the upper lobe.

of the right lung but none was visualized there. Bronchoscopic examination showed edema of the bronchus on the right side, with hypertrophy of the mucosa, so that the bronchoscope could not be passed further. Bronchoscopic aspiration was performed. The material thus obtained showed numerous various-sized cells with oval nuclei and light, irregularly staining protoplasm. Some of the cells were of the columnar variety, most, however, resembled the oat cell seen in cases of bronchogenic carcinoma.

*Comment*—When pneumonia develops in a patient of "cancer age" and assumes an abnormal course, the possibility of an underlying carcinomatous process must be entertained.

Case 11 demonstrates the value of exploratory thoracotomy and biopsy of questionable tissue.

CASE 11—M. L., a man aged 52 years, was admitted on May 16, 1926, complaining of pain in the right side of the chest for four days. The onset of the pain was sudden and was followed by dyspnea and daily elevations in temperature to 103 F, chills and persistent cough. Three months previous to the present illness the patient had pain in the right shoulder and swelling of the right arm for several days.

Examination showed an acutely sick patient who was somewhat cyanotic about the lips. There were dullness and absence of breath sounds over the lower right half of the pulmonary field, above which there were signs of pneumothorax. The blood count showed 30,000 white cells, with a differential count of 85 per cent polymorphonuclears and 15 per cent lymphocytes. The hemoglobin value was 60 per cent, and the red blood cells totaled 3,800,000. On entry a roentgenogram showed hydropneumothorax on the right side. The underlying lung was infiltrated. Thoracotomy was performed, relieving the patient of some pus but not relieving the symptoms. A postoperative roentgenogram failed to show any appreciable changes. Another thoracotomy was performed, with exploration of the chest. The lung was found to be adherent locally, indurated in some areas and soft in others. The latter areas were pearly gray. Some of this soft tissue was removed, and microscopic examination revealed adenocarcinomatous changes.

*Comment*—When a patient of "cancer age," without apparent cause, shows spontaneous pneumothorax or empyema and fails to rally after the proper therapy is instituted, the diagnosis of carcinoma of the lung must be entertained until ruled out.

#### COMMENT AND CONCLUSIONS

There is no doubt that a certain number of cases of carcinoma of the lung will continue to escape recognition until late in the course of the disease, not merely because patients are prone to delay medical consultation and because the disease produces symptoms mimicking those of other diseases and therefore is not readily recognized but because the first symptoms to attract the patient's attention are due to metastatic deposits. In our own cases epigastric distress, nausea, vomiting, pruritis, dysuria and hemorrhoids were not infrequently

encountered as the initial complaints. In 13 (21.6 per cent) of our cases the first symptoms which brought the patient to the physician did not suggest an intrathoracic new growth. In most of these cases a routine roentgenographic study unexpectedly revealed an intrathoracic pathologic condition which was later diagnosed as primary carcinoma of the lung.

In reviewing our cases we feel that in at least 10 of the 18 cases in which the diagnosis was not established until one month to six months had elapsed after the patient had first sought medical advice, the correct diagnosis would have been made if the physician had thought of the fact that infradiaphragmatic symptoms are often due to a supradiaphragmatic pathologic condition or, in the suspicious case, if the physician had suggested bronchoscopic examination as an aid in making the diagnosis. A painstaking study of the history would have suggested the possibility of carcinoma of the lung, particularly in those cases in which there had been intermittent periods of dyspnea, a change in the patient's habit of coughing or a change in the character of the expectoration. A more careful physical examination in cases in which the cause of the disorder was obscure, particularly in the patient of "cancer age," would have been of inestimable value.

The crux of the problem of carcinoma of the lung lies in its consideration in every case of an obscure ailment. The general practitioner who first encounters a combination of suspicious symptoms and signs in the course of an examination of the chest owes it to himself and to his patient to seek authoritative opinion or to persist in his investigation until a final satisfactory diagnosis is established. In the investigation of such cases roentgenographic and bronchographic studies, bronchoscopic examination and biopsy of tissue removed bronchoscopically are of the utmost importance. Negative results of studies should not be considered as excluding the possibility of bronchogenic carcinoma. In 1 of our cases the early roentgen and bronchographic studies did not suggest carcinoma of the lung, the bronchoscopic findings suggested "bronchial stenosis," and tissue removed bronchoscopically was reported as being "chronic inflammatory tissue." A restudy two weeks later did not yield any further information. But, because of the history and the altered breathing in one area of the lung, the clinician persisted in his belief that carcinoma was present. Biopsy tissue removed bronchoscopically one week later was reported as containing "carcinomatous tissue." Occasionally such studies as those mentioned will yield doubtful results and leave one still suspicious of the presence of carcinoma. In such instances, exploratory thoracotomy should be performed. Adler, as early as 1912, stated

As at the present the conscientious physician examines every chest for possible tuberculosis, so in the future every chest will have to be examined for possible tumor. The writer would go still further. Where all the means of diagnosis outlined in this little study fail, where there is suspicion of tumor, but no assurance is possible, there should be,—it is emphatically here stated,—as little hesitation in resorting to an exploratory thoracotomy as there is nowadays in submitting to an exploratory laparotomy.

Today, twenty-five years later, with the advances in thoracic surgery and intratracheal anesthesia, exploratory thoracotomy should not be considered any more dangerous than exploratory laparotomy. At the time of exploratory thoracotomy some of the suspicious tissue can be removed and examined microscopically.

The future of the management of carcinoma of the lung depends in a large measure on its early recognition. Thoracic surgery has advanced much farther than has the ability of the practitioner to make an early diagnosis of bronchogenic carcinoma, judging from the patients with so-called early carcinoma who are submitted to surgeons. If the diagnosis is to be made early it must be borne in mind that relatively trivial symptoms are important and that a disease within the thorax may produce extrathoracic symptoms.

From the foregoing consideration the following conclusions may be listed:

Carcinoma of the lung is not an uncommon disease.

In 21.7 per cent of our 60 cases no symptoms referable to the thorax were presented.

In 81.8 per cent of our cases the patients were between 45 and 65 years of age.

The disease is almost four times as frequent in males as it is in females.

There are no signs or symptoms pathognomonic of early carcinoma of the lung. A change in the habit of coughing or in the character of the expectoration or paroxysmal dyspnea without apparent cause requires a careful examination of the thorax before carcinoma of the lung is ruled out.

If the possibility of malignant growth elsewhere has been ruled out, the final diagnosis of bronchogenic carcinoma rests with the microscopic observation of malignant cells in representative tissue.

The accessory means of diagnosis of early carcinoma of the bronchus, in the order of facility and diagnostic importance, are (*a*) bronchoscopic examination and biopsy of tissue removed bronchoscopically, (*b*) study of the pleural effusion, (*c*) puncture of the lung, (*d*) exploratory thoracotomy and (*e*) biopsy of an accessible metastatic nodule.



# ARTERIOLES OF THE PANCREAS, LIVER, GASTRO- INTESTINAL TRACT AND SPLEEN IN HYPERTENSION

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Bright's<sup>1</sup> epoch-making observation in 1836 of the association of cardiac hypertrophy with renal disease assumed new significance in 1868, when Johnson<sup>2</sup> noted coexistent thickening of the arterial walls in this condition. That renal damage need not necessarily precede the other two factors was pointed out by Mahomed<sup>3</sup> in 1874 and later was substantiated by Allbutt<sup>4</sup>.

Subsequent to these fundamental observations, continued study has emphasized more and more that of the whole vascular tree, the arteriolar bed suffers most profoundly from the changes that are known to be rather characteristically associated with hypertension. This is not surprising, because Landis<sup>5</sup> noted that the greatest pressure gradient in the frog and in the mammalian mesentery is in the arteriole and Ellis and Weiss<sup>6</sup> found that with an increase in vascular tension the load of work carried by the arteriole is magnified relatively many more times than is that of any other part of the vascular bed.

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From the Division of Medicine of the Mayo Clinic

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4 Allbutt, T. C., cited by Cowdry, E. V. Arteriosclerosis. A Survey of the Problem, New York, The Macmillan Company, 1933, p. 49

5 Landis, E. M. The Capillary Pressure in Frog Mesentery as Determined by Micro-Injection Methods, *Am J Physiol* **75** 548-570 (Feb.) 1926, Micro-Injection Studies of Capillary Pressure in Mammalian Mesentery, *ibid* **85** 387 (June) 1928

6 Ellis, L. B., and Weiss, S. The Measurement of Capillary Pressure Under Natural Conditions and After Arteriolar Dilatation in Normal Subjects and in Patients with Arterial Hypertension and with Arteriosclerosis, *J Clin Investigation* **8** 47-67 (Dec.) 1929

Authors have not been in agreement as to the relative frequency of arteriolar changes in the different tissues of hypertensive patients.<sup>7</sup> The wide divergence of opinion results partly because criteria for evaluation of changes in vessels have varied greatly and partly because standard methods for classification of hypertension have not been used. It is reasonable to infer that the clinical severity of the hypertension and the duration of the disease are factors important in determining the degree of vascular change. Hence it is imperative that more accurate criteria for delimiting hypertension be used and that, if possible, the conditions be grouped by virtue of certain measurable factors into classes according to the severity of the involvement. Thus, the small artery and the arteriole should be studied, and an attempt should be made to relate the definite pathologic picture which a given vessel presents to the degree of severity of hypertension suffered by the patient so that it may be determined whether or not the observed changes mark the most severely hypertensive patient as distinct from one less severely hypertensive, just as certain measurable features characterize the vessel of a person who has a normal blood pressure.

Such an attempt was made first by Kernohan, Anderson and Keith, in 1929.<sup>8</sup> They studied the arteriole of pectoral muscle at biopsy. Specimens were obtained from hypertensive patients who, on the basis of arbitrary clinical standards, had been grouped according to the severity of the disease. In the vessels of the pectoral muscle of hypertensive patients they found a measurable deviation from normal that was most marked when histologic change was most evident and in those patients who had the most severe disease clinically. Andrus,<sup>9</sup> by study of material obtained at necropsy, was unable to verify the conclusions of Kernohan and his co-workers, he expressed the belief that postmortem change and structural alteration of vessels after death made measurement of the wall of the vessel valueless and concluded that a study of the arteriole of pectoral muscle gave no accurate hint of the degree of clinical hypertension. His work lacks conviction because the clinical standards he used for the diagnosis of hypertension were not rigid.

Moritz and Oldt,<sup>10</sup> from an exceedingly comprehensive survey, concluded that neither the physiologic state of the vascular system at the time the specimens were obtained nor variation in the methods used in

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7 In this paper the term hypertensive patient refers to a patient who has diffuse arteriolar disease and hypertension.

8 Kernohan, J. W., Anderson, E. W., and Keith, N. M. The Arterioles in Cases of Hypertension, *Arch. Int. Med.* **44**: 395-423 (Sept.) 1929.

9 Andrus, F. C. The Relation of Age and Hypertension to the Structure of the Small Arteries and Arterioles in Skeletal Muscle, *Am. J. Path.* **12**: 635-652 (Sept.) 1936.

10 Moritz, A. R., and Oldt, M. R. Arteriolar Sclerosis in Hypertensive and Non-Hypertensive Individuals, *Am. J. Path.* **13**: 679-728 (Sept.) 1937.

preparing tissues for microscopic examination led to changes in arteriolar dimensions that were greater than those resulting from anatomic variations or errors in mensuration under controlled conditions. They also expressed the opinion that a numerical value useful in distinguishing hypertensive from nonhypertensive persons is obtained from the mean external diameter of arterioles within a fixed range of size. One of the most significant facts they brought out is that the thickness of the wall and the caliber of the lumen do not bear a constant relation to each other throughout the length of a diseased vessel.

I have made a histologic study of the arteriolar bed of the liver, pancreas, spleen and the gastrointestinal tract of hypertensive patients thereby hoping to contribute something to the knowledge of the relation of vascular pathologic conditions to hypertension. Heretofore, conclusions concerning this relation have been drawn from impressions obtained by study of a comparatively limited amount of tissue and of few controls. I felt that tissue specimens from an adequate series of patients in conjunction with specimens from a sufficient number of controls studied histologically with differential stains and analyzed by mathematically precise methods would give valuable information.

#### METHOD

Tissue was obtained routinely at necropsy from both the normal and the hypertensive persons. The tissue was fixed in a dilute solution of formaldehyde U. S. P. (1:10), blocked in paraffin and stained. Measurements were made of the vessels in tissue stained by the hematoxylin and eosin method. Histologic evaluation of changes in vessels was made with the aid of the Van Gieson, the Heidenhain modification of the Mallory, the elastin H and the scarlet red differential stain. Of these the Van Gieson stain for differentiation of fibrous and muscular elements and the elastin H stain for recognition of elastic tissue proved to be most useful.

Although the value of measuring arterioles in histologic material has been seriously questioned by Andrus, I believe, after careful evaluation of laboratory methods as a factor of error, that the conclusions of Moritz and Oldt give justification for this method. Therefore, I do not believe that laboratory methods will be a significant factor in the interpretation of my findings. Moreover, if an error was introduced, since specimens from both the normal and the hypertensive persons were subjected to similar methods and since the value of this study lies in comparative measurements, I believe that such an error would become nonactive and could be disregarded.

For the measurement of the wall of the vessel and for computation of the ratio of the thickness of the wall to the diameter of the lumen, a Bausch and Lomb micrometer eyepiece was used over an objective of high power, giving a magnification of 450. The wall of each vessel was measured in four places (fig. 1, *ab*, *cd*, *ef* and *gh*) and the lumen in two diameters (*bc* and *fg*), and the average for the wall and the lumen of each vessel was then obtained. Each measurement was made to the nearest 0.005 mm. Only vessels which were cut at right angles to their course were measured. Six vessels in each section were measured, and the average of these was assumed to be a fair estimate of a vessel representative of that tissue. I have adopted Kernohan's criteria and have considered as an arteriole any vessel the outside diameter of which is between 25 and 100 microns.

## NORMAL SUBJECTS

The ratio of the thickness of the arteriolar wall to the diameter of the lumen first had to be established for each of the tissues of normal subjects. Sixty patients ranging in age from 20 to 79 years and equally divided into six age groups were selected as controls with respect to each tissue. I made no effort to distinguish between the two sexes. Death in these cases had been caused by a wide range of conditions, neoplasm predominating. Specimens from obese persons were not included, each patient had weighed less than 180 pounds (81.6 Kg). There was neither clinical nor pathologic evidence that hypertension had existed in any of these patients. Clinical evidence included an unimportant personal history and a systolic blood pressure which did not

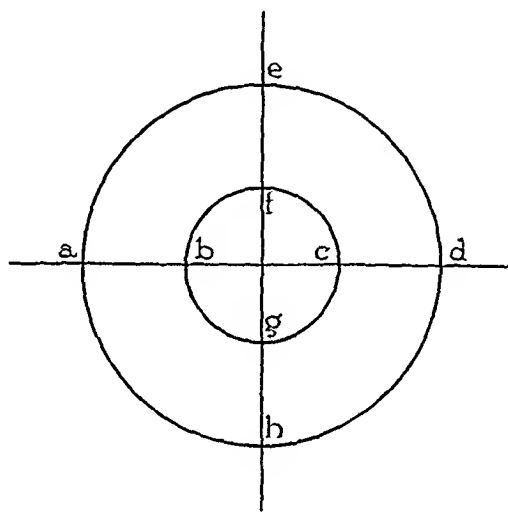


Fig 1—Cross section of arteriole. The thickness of the wall was obtained by averaging *ab*, *cd*, *ef* and *gh*. The diameter of the lumen was obtained by averaging *bc* and *fg*.

exceed 140 mm of mercury. Because it has been shown rather definitely that age is not a factor of importance in determining the size of the heart and that cardiac hypertrophy depends on the height at which it has been necessary to sustain the blood pressure during life,<sup>11</sup> a heart of normal weight was interpreted as evidence of a preexisting normal blood pressure. For these controls the weight of the heart was between the upper and the lower limit of normal, as calculated by Smith's<sup>11</sup> formula. Cases in which the cardiac weight exceeded 400 Gm were not considered.

<sup>11</sup> Smith, H. L. The Relation of the Weight of the Heart to the Weight of the Body and of the Weight of the Heart to Age, *Am Heart J* 4: 79-93 (Oct) 1928.

## HYPERTENSIVE PATIENTS

In all cases the history was carefully recorded, and physical examination, measurement of blood pressure, a record of the appearance of the retina, and tests of renal and cardiac function were made. In most cases electrocardiographic tracings were obtained.

Retinal observations deserve special mention because the severity of changes noted in the fundus of the eye played a large part in the clinical grouping of the patients. Because the retinal and choroidal vessels are arterioles and because changes in these vessels probably are indicative of similar changes in vessels of like size in other parts of the body, the significance of the condition of these vessels is at once apparent. The most severe degree of hypertension, so-called malignant hypertension or malignant nephrosclerosis, is associated with a distinctive appearance of the fundus, which has been described in detail by Wagener<sup>12</sup>. In such cases examination of the fundus usually gives evidence of a severe degree of arteriolar narrowing and sclerosis, characteristic retinitis with retinal edema, cotton-wool exudate, hemorrhagic regions and papilledema. Papilledema is a striking feature, and always is present in minor or major degree, it may reach an elevation of 6 D and may be disproportionate to other changes in the retina.

I have classified the hypertensive patients into three groups, which correspond to groups 2, 3 and 4 outlined by Keith, Barker and Kernohan<sup>13</sup>. That arbitrary grouping is justifiable was indicated by the pathologic data compiled by Kernohan, Anderson and Keith in 1929 and has been borne out subsequently by clinical experience.

*Group 1*—The patients comprising this group often are spoken of as having benign hypertension. The systolic blood pressure is elevated definitely and persistently above the level of 140 mm of mercury. There is no evidence of renal or of cardiac damage, and examination of the retinal arterioles reveals only a minimal degree of sclerosis and narrowing (grade 1, on the basis of 1 to 4). Keith and his co-workers found that in the arterioles of pectoral muscle the ratio of the thickness of the wall to the diameter of the lumen was usually reduced as compared with the normal ratio. The disease may remain stationary for a

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12 Wagener, H. P. The Retinitis of Malignant Hypertension, *Tr. Am. Ophth. Soc.* **25** 349-380, 1927, Retinal Vascular Changes in Hypertension, *Ann. Int. Med.* **4** 222-226 (Sept.) 1930. Wagener, H. P., and Keith, N. M. Cases of Marked Hypertension, Adequate Renal Function and Neuroretinitis, *Arch. Int. Med.* **34** 374-387 (Sept.) 1924.

13 Keith, N. M., Barker, N. W., and Kernohan, J. W. Histologic Studies of the Arterioles in Various Types of Hypertension, abstracted, *Tr. A. Am. Physicians* **46** 66-70, 1931.

long time, or it may progress to more serious forms of hypertension. None of the patients belonging in this group who came to necropsy were included in the present study.

*Group 2*—In patients belonging to this group Keith and his co-workers observed a more marked alteration in the ratio of wall to lumen as compared with the normal value. They noted more pronounced retinal arteriolar sclerosis (grade 2) but no actual retinal, cerebral, cardiac or renal insufficiency. In this group the blood pressure was higher than in group 1. The systolic blood pressure was sometimes much more than 200 mm of mercury, and it fluctuated to a normal level less often than in the patients in group 1.

I found 9 patients who showed conformity with these requirements. Eight of these patients were men, and 1 was a woman, their ages ranging from 49 to 71 years. Knowledge on the part of the patient concerning the existence of hypertension varied; patients had known of their illness usually for several years. In 1 instance in which life was terminated by cerebral thrombosis, hypertension had been present for thirty years. The systolic blood pressure was at least 190 mm of mercury and the diastolic blood pressure 110 mm of mercury in every case. In 1 case a systolic peak of 255 mm of mercury was reached. The heart was demonstrably enlarged, and there were an apical systolic murmur and accentuation of the closure of the aortic semilunar valve in all cases. Electrocardiographic examination gave evidence of significant changes, interpreted as characteristic of hypertension,<sup>14</sup> in some instances. Examination of the fundi gave evidence of sclerosis and narrowing of the retinal arterioles, in 1 case being of grade 1, in 7 cases of grade 2 and in 1 case of grade 3. Peripheral arterial sclerosis was variable, being of grade 3 in 4 cases. In all cases albuminuria was present, in 4 cases being of grade 1, in 4 cases of grade 2 and in 1 case of grade 3. The concentration of urea in the blood at the time of examination was normal for the entire group. In no case was there evidence of anemia which could be attributed solely to the hypertension. Death was caused by intercurrent disease in 5 cases, by cerebrovascular occlusion in 2 cases, by myocardial failure in 1 case and by pulmonary embolism in 1 case. The following case is typical.

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14 Rykert, H. E., and Hepburn, J. Electrocardiographic Abnormalities Characteristic of Certain Cases of Arterial Hypertension, *Am Heart J* **10** 942-954 (Oct.) 1935. Wilhous, F. A. Observations on the Negativity of the Final Ventricular T Wave of the Electrocardiogram, *Am J M Sc* **160** 844-865 (Dec.) 1920, Electrocardiography and Prognosis. I. Significant T Wave Negativity in Isolated and Combined Derivations of the Electrocardiogram, *Arch Int Med* **30** 434-450 (Oct.) 1922.

CASE 1—A man aged 68 years, a minister of English extraction, had had hypertension for thirty years. There was no history of cardiac or of vascular disease in his family. His previous illnesses included scarlet fever, rheumatic fever and influenza. Eleven years prior to death his blood pressure was 178 systolic and 120 diastolic. He suffered from dyspnea and occasional precordial distress. On entry his systolic blood pressure varied between 190 and 212 mm of mercury and the diastolic pressure between 120 and 130 mm of mercury. There were cardiac hypertrophy and peripheral sclerosis (grade 3). There was albuminuria (grade 1), the concentration of urea in the blood was 48 mg per hundred cubic centimeters, the flocculation test of the blood for syphilis gave negative results and anemia was not present. Electrocardiographic examination gave evidence of preponderance of the left ventricle and of inversion of the T wave in lead I. Examination of the fundi gave evidence of arteriolar sclerosis (grade 2), and of narrowing of the vessels. Death was caused by thrombosis of the basilar artery with cerebral infarction. Significant conditions observed at necropsy, in addition to cerebral infarction, were hypertrophy of the heart (weight, 538 Gm), renal atrophy and generalized arteriosclerosis.

*Group 3*—Keith and his co-workers said that the status of the patients in this group is characterized by marked hypertension, by more pronounced arteriolar sclerosis of the retinal vessels than that observed in group 2, by vasospastic retinitis, in some cases by functional cerebral, cardiac and renal insufficiency and by an average ratio of wall to lumen in the arterioles of pectoral muscle of 1:1.4.

I studied 14 patients belonging to this group, 8 were men and 6 were women. They ranged in age from 36 to 69 years. The criteria which were met by each patient of this group were (1) a persistently high systolic and diastolic pressure, with a tendency toward fixation, (2) myocardial change, as evidenced by measurable clinical cardiac enlargement, by electrocardiographic evidence of preponderance of the left ventricle and by significant alteration of the T wave, (3) moderate to severe renal damage, with albuminuria and sometimes with elevation of the concentration of urea in the blood, and (4) characteristic changes in the retina, comprising moderately severe narrowing and sclerosis of the retinal arterioles, retinitis with exudate and hemorrhage but not edema of the disk.

Most of the patients in this group had been aware of preexisting hypertension for a number of years, 2 of them for as long as ten years. The maximal systolic blood pressure in all but 2 cases was 200 mm of mercury or greater. The heart was demonstrably enlarged on percussion in every case, and an apical systolic murmur was audible. Peripheral sclerosis was of grade 2 in 5 cases and of grade 3 in 6. Arteriolar sclerosis of the vessels of the fundi was of grades 1 to 3, the majority of patients having severe involvement. Definite anemia, as evidenced by low concentration of hemoglobin, was encountered in 50 per cent of the cases. Relatively severe renal involvement was demonstrable before death in every case. Albuminuria of grade 1 was present in 2

cases, of grade 2 in 2 cases, of grade 3 in 7 cases and of grade 4 in 3 cases. The concentration of urea in the blood was less than 40 mg per hundred cubic centimeters in only 1 case and rose to a maximum of 354 mg in 1 instance. Death was caused by renal failure in 7 cases, by myocardial failure in 5, by intercurrent infection in 1 and by cerebrovascular hemorrhage in 1. The following case is typical.

**CASE 2**—The patient was a woman aged 36 years. There was no history of hypertensive disease in the family. Her previous illnesses were pneumonia, influenza, tonsillitis and toxemia of pregnancy. She had been aware of hypertension and albuminuria for three years, the symptoms being weakness, epigastric distress, vomiting, headache and visual failure. Physical examination showed restlessness, pallor, cardiac enlargement with an apical systolic murmur and bilateral basilar rales. The margin of the liver was 12 cm below the costal arch. There was pretibial edema. The blood pressure varied between 190 and 260 mm of mercury systolic and between 105 and 150 mm of mercury diastolic. There were fixation of the specific gravity of the urine and albuminuria (grade 3). The concentration of urea in the blood was 354 mg per hundred cubic centimeters. Secondary anemia was marked, and the concentration of hemoglobin was 5.6 Gm per hundred cubic centimeters. The flocculation test of the blood for syphilis gave negative results. Peripheral sclerosis (grade 2) was present. Examination of the fundi gave evidence of severe angiospasm of the retinal and choroidal arterioles, with hemorrhages and cotton-wool exudates. Narrowing of the vessels was of grade 3, and sclerosis was of grade 2. Electrocardiographic examination gave evidence of an isoelectric T wave in lead I and a diphaseic T wave in lead II. Death was caused by renal failure. The significant observations at necropsy were renal atrophy, cerebral infarction, acute pericarditis, hydrothorax, ascites and hypertrophy of the heart (weight, 433 Gm).

**Group 4**—The condition in patients belonging to this group may represent an end stage of a disease of which the first three groups of patients exhibit the less severe forms, or it may be a distinct entity<sup>15</sup>. It has been variously termed malignant nephrosclerosis<sup>16</sup> and malignant hypertension<sup>17</sup>. Keith, Wagener and Kernohan showed that the most significant lesion associated with this disease was diffuse arteriolar

15 Koenigsberger, C., Bannick, E. G., and Beaver, D. C. Acute Vasospastic Hypertensive Disease with Transition into Malignant Hypertension. Final Report of a Case with Necropsy, *Minnesota Med* **16** 186-192 (March) 1933. Amberg, S. Hypertension in the Young, *Am J Dis Child* **37** 335-350 (Feb.) 1929. Craig, J. Malignant Hypertension in Childhood, *Arch Dis Childhood* **6** 157-164 (June) 1931.

16 Klemperer, P., and Otani, S. Malignant Nephrosclerosis (Fahr), *Arch Path* **11** 60-117 (Jan.) 1931. Fahr, T. Ueber maligne Nierensklerose (Kombinationsform), *Centralbl f allg Path u path Anat* **27** 481-498, 1916. MacMahon, H. E., and Pratt, J. H. Malignant Nephrosclerosis (Malignant Hypertension) *Am J M Sc* **189** 221-235 (Feb.) 1935.

17 Vollhard, F. Die doppelseitigen hamatogenen Nierenerkrankungen (Bright'sche Krankheit), Berlin, Julius Springer, 1918. Keith, N. M., Wagener, H. P., and Kernohan, J. W. The Syndrome of Malignant Hypertension *Arch Int Med* **41** 141-188 (Feb.) 1928.



sclerosis, and in 1929 Keimohan, Anderson and Keith showed that in this group the mean ratio of wall to lumen in the arteriole of pectoral muscle was 1 : 1.

Clinically in these cases the readings of systolic and diastolic pressure are high and do not fluctuate to normal levels even with complete rest. There is a severe degree of sclerosis of the peripheral arteries. The involvement of the heart and kidneys is very marked, and there are symptoms of failure of these organs. The retinal picture is the most important single factor in distinguishing this group from the others. There is a severe degree of sclerosis, narrowing of the arterioles and distinctive neuroretinitis accompanied by papilledema and visual failure. Keith<sup>18</sup> said he believed that despite the diffuse character of the lesion, one organ is predominantly involved and that this factor permits classification of the disease into (1) the cerebral type, in which attacks of hemiplegia are characteristic and cause death, (2) the cardiac type, in which the signs of cardiac failure predominate, with anginal attacks, pulmonary edema and generalized anasarca, and (3) the renal type, in which signs of a rapidly fatal renal failure are predominant. Characteristically, however, in the end stages there may be a combination of cerebral, retinal, cardiac and renal failure.

There were 43 patients in this group in my series, 31 were men and 12 women. They ranged in age from 22 to 75 years, the majority being from 35 to 55 years old. Few of them had been aware of pre-existing hypertension for more than a short time prior to death. In 1 case there was a history of hypertension of eight years' duration, but this was unusual, the striking characteristic was the rapidly fatal outcome after the discovery of abnormal arterial tension.

The maximal systolic blood pressure was less than 200 mm of mercury in only 4 cases. The highest systolic pressure recorded, in 1 instance, was 170 mm of mercury. The highest systolic pressure for the group was 350 mm of mercury. Peripheral sclerosis was severe in every case. There was clinical evidence of myocardial damage and failure. Electrocardiographic examination revealed significant alterations in the T wave in 29 cases. Retinitis and edema of the fundi were present in every case, the greatest degree of papilledema recorded was 4 D. Sclerosis of the retinal vessels of grade 2 was present in 23 cases and of grade 3 in 20 cases. Marked renal impairment was indicated by the presence of fixation of the specific gravity of the urine and albuminuria. Albuminuria of grade 4 was present in 11 cases, of grade 3 in 15 cases, of grade 2 in 10 and of grade 1 in 7. The concentration of urea in the blood was less than 40 mg per hundred cubic centimeters in only 6

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18 Keith, N. M. Classification of Hypertension and Clinical Differentiation of the Malignant Type, *Am Heart J* 2: 597-608 (Aug.) 1927.

cases and reached the high concentration of 657 mg in 1 case. Definite anemia was present in 65 per cent of the cases. Death was caused by renal failure in 26 cases, myocardial failure in 4, cerebrovascular accident in 6, intercurrent infection in 5 and gastrointestinal hemorrhage in 2. The following case is typical.

**CASE 3**—The patient was a man aged 29 years. His father died of cerebral hemorrhage, his mother had hypertension. He had scarlet fever at the age of 15 years, other illnesses were smallpox, measles, chickenpox, mumps and diphtheria. Hypertension was discovered eight months before his admission to the hospital, when he sought advice because of failing vision. Subsequent symptoms were headache, nausea, vomiting, edema and loss of weight. He was thin and pale. Generalized peripheral sclerosis (grade 3) was present. The heart was enlarged, and there was a soft aortic systolic murmur. Examination of the fundi gave evidence of severe sclerosis (grade 3), of angiospastic retinitis and of bilateral papilledema of 3 D. Electrocardiographic examination gave evidence of a diphasic T wave in lead I. The blood pressure varied from 168 to 240 mm of mercury systolic and from 104 to 150 mm diastolic. There was a tendency toward fixation of the specific gravity of the urine, and there was albuminuria (grade 3). The concentration of urea in the blood was 492 mg per hundred cubic centimeters. The concentration of hemoglobin was 8.5 Gm per hundred cubic centimeters, and the flocculation test of the blood for syphilis gave negative results. The disease progressed rapidly, and death was caused by renal failure. At necropsy, hypertrophy of the heart (weight, 405 Gm), marked renal atrophy, pericarditis and multiple cerebral petechiae were observed.

#### RATIO OF WALL TO LUMEN OF THE NORMAL ARTERIOLE

The four organs were studied in each of the 60 controls, and the mean ratio of wall to lumen in each case was determined. There was equal division of the patients into six age groups, ranging from the ages of 20 to 79 years. The mean ratio for each age group and that

TABLE 1—*Mean Ratio of the Thickness of the Wall to the Diameter of the Lumen of the Arterioles of Normal Subjects*

Age Group	Pancreas	Liver	Gastrointestinal Tract	Spleen
20-29	1.244	1.231	1.219	1.130
30-39	1.243	1.233	1.210	1.132
40-49	1.242	1.223	1.215	1.139
50-59	1.236	1.237	1.213	1.127
60-69	1.253	1.234	1.213	1.136
70-79	1.254	1.229	1.211	1.131
Mean ratio for whole group	1.245	1.231	1.213	1.132

for the whole group are recorded in table 1. It is immediately evident that age does not alter the ratio in any tissue, because the ratio is essentially identical for all age groups.

In the pancreas the lowest ratio was 1.204, the highest was 1.307 and the mean was 1.245. In the liver the lowest ratio was 1.187, the highest was 1.286 and the mean was 1.231. In the gastro-

intestinal tract the lowest ratio was 1.189, the highest was 1.244 and the mean was 1.213. For this tissue, in the normal persons as well as in the hypertensive patients, no single isolated portion was taken, but any part from the esophagus to the rectum was considered as representative. In the spleen the lowest ratio was 1.104, the highest was 1.16 and the mean was 1.132.

These results agree fundamentally with the normal values other workers have used, and, with the exception of the spleen, the ratio is approximately 1.2, which is the ratio which Kernohan and his co-workers concluded was normal for all tissues.

#### MEASUREMENTS OF ARTERIOLES OF HYPERTENSIVE PATIENTS

*Group 2*—There were only 9 patients in this group, insufficient for subdivision into different age groups.

In the pancreas the lowest ratio of wall to lumen was 1.133, the highest was 1.193 and the mean was 1.163. In the liver the lowest

TABLE 2—*Mean Ratio of the Thickness of the Wall to the Diameter of the Lumen of the Arterioles of Normal Subjects in Comparison with the Corresponding Ratio of the Arterioles of Hypertensive Patients*

Organ	Controls	Group 2	Group 3	Group 4
Pancreas	1.245	1.163	1.133	1.124
Liver	1.231	1.171	1.133	1.114
Gastrointestinal tract	1.213	1.156	1.115	1.114
Spleen	1.132	1.124	1.109	1.104

ratio was 1.151, the highest was 1.183 and the mean was 1.171. In the gastrointestinal tract the lowest ratio was 1.37, the highest was 1.175 and the mean was 1.156. In the spleen the lowest ratio was 1.099, the highest was 1.147 and the mean was 1.124.

By reference to table 2, it is evident that the ratio of wall to lumen in this group is altered distinctly in each tissue as compared with the normal. This alteration is brought about by thickening of the arteriolar wall and by reduction of the caliber of the lumen.

*Group 3*—In this group were included 10 patients for each tissue studied, except that tissue representative of the gastrointestinal tract was studied in only 7 cases.

In the pancreas the lowest ratio of wall to lumen was 1.117, the highest was 1.151 and the mean was 1.133. In the liver the lowest ratio was 1.11, the highest was 1.16 and the mean was 1.133. In the gastrointestinal tract the lowest ratio was 1.101, the highest was 1.132 and the mean was 1.115. In the spleen the lowest ratio was 1.084, the highest was 1.126 and the mean was 1.109.

When the mean value for each tissue is compared with the normal value, the great alteration of the ratio incident to hypertension is evident (table 2)

*Group 4*,—There were 43 patients in this group, a sufficient number to make it possible to subclassify them into different groups according to age, as was done for the normal persons. The results when tabulated (table 3) indicate that, as in normal persons, in hypertensive patients age has no bearing on the ratio of the thickness of the wall of the arteriole to the diameter of its lumen.

In the pancreas the lowest ratio was 1.094, the highest was 1.161 and the mean was 1.124. In the liver the lowest ratio was 1.09, the highest was 1.161 and the mean was 1.114. In the gastrointestinal tract (this tissue was obtained from only 18 patients), the lowest ratio was 1.1, the highest ratio was 1.142 and the mean was 1.114. In the spleen the lowest ratio was 1.085, the highest was 1.124 and the mean was 1.104.

TABLE 3—*Mean Ratio of the Thickness of the Wall to the Diameter of the Lumen of the Arterioles of the Hypertensive Patients of Group 4*

Age Group	Pancreas	Liver	Gastrointestinal Tract	Spleen
20-29	1.123	1.111	1.109	1.105
30-39	1.131	1.117	1.113	1.111
40-49	1.125	1.115	1.115	1.104
50-59	1.126	1.116	1.115	1.104
60-69	1.096	1.102		1.098
70-79	1.120	1.118		1.094
Mean ratio for whole group	1.124	1.114	1.114	1.104

By referring again to table 2, the uniform alteration of the ratio for each tissue from the different groups of hypertensive patients as compared with the normal values is readily apparent. This alteration is greatest in the groups of the more severely hypertensive patients (groups 3 and 4), hence it seems reasonable to assume that the thickness of the wall of the arteriole and its relation to the diameter of the lumen of the arteriole are directly dependent on the severity of the disease. The effect of hypertension is widespread and affects all the tissues studied. Even in the spleen there are definite, consistent alterations, although its arterioles normally have a thick wall and, it seems, are better able to withstand the burden of increased vascular tension than are the arterioles of other organs.

Figures 2 to 5 are graphic representations of the ratio of the thickness of the wall of the arteriole to the diameter of its lumen for all the patients. Each point represents a measured ratio of wall to lumen in 1 case. To indicate the mean about which the values for each group of hypertensive patients and normal subjects are arranged, lines have

been drawn from zero through the point which represents the mean for that group. There is practically no overlapping of the values for the normal and the hypertensive subjects except in the case of the spleen. This is not surprising, because in the spleen the difference between the ratio for the normal arteriole and that for arterioles representative of those of the patients in group 4 is not particularly great. These figures indicate that because the points have a relatively narrow dispersion, the changes are not those which affect isolated vessels, rather, they are those

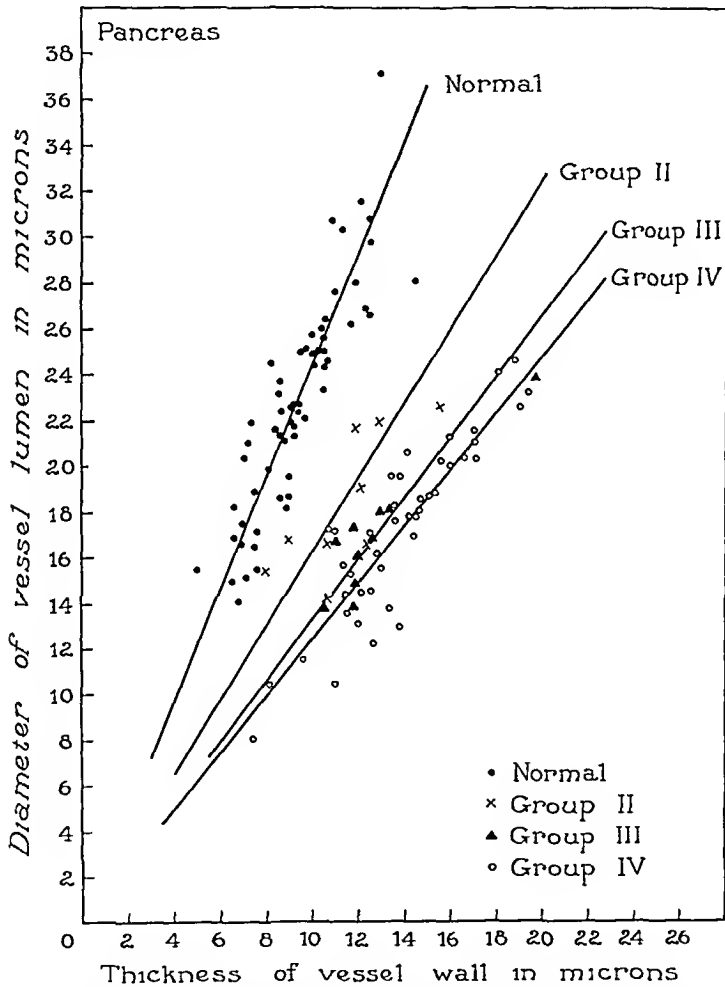


Fig 2—Ratio of the thickness of the wall to the diameter of the lumen in the arterioles of the pancreas. The continuous lines represent the mean ratios for each group.

which affect uniformly all vessels of equal size. Because the angle which the line representing mean values subtends with the abscissa is representative of the ratio of wall to lumen, it is evident that an identical situation exists for the arterioles of all tissues studied, namely, that the greatest deviation of the ratio from normal uniformly depends on the severity of the disease. The patients in group 4 showed a ratio

of nearly 1 : 1, those in group 2, a ratio nearest normal (1 : 2), although it was likewise definitely altered. The ratios for the patients in group 3 were little different from those for the patients in group 4 but were distinctive enough to lend pathologic justification to such a clinical grouping.

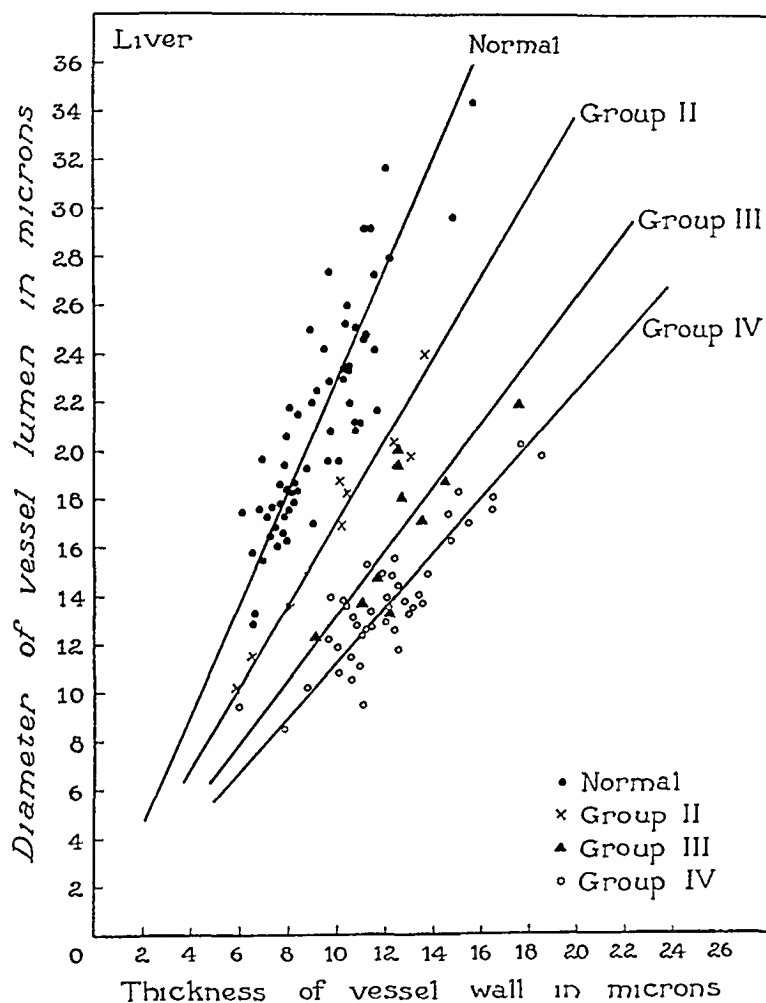


Fig. 3—Ratio of the thickness of the wall to the diameter of the lumen in the arterioles of the liver

#### HISTOLOGIC CHANGE IN THE ARTERIOLE

Interpretation of histopathologic change in the arteriole in hypertensive patients has provoked much controversy among students of this subject. There has not been uniform agreement that Johnson was correct in his original view, that the important change was hyperplasia and hypertrophy of the muscular elements of the media, or that Gull and Sutton<sup>19</sup> were correct in their observance of the predominance of hyaline, fibroid degeneration.

<sup>19</sup> Gull, W. W., and Sutton, N. G. On the Pathology of the Morbid State Commonly Called Chronic Bright's Disease with Contracted Kidney ("Arterio-capillary Fibrosis"), *Tr. Roy. Med.-Chir. Soc.* 55: 273-326, 1872.

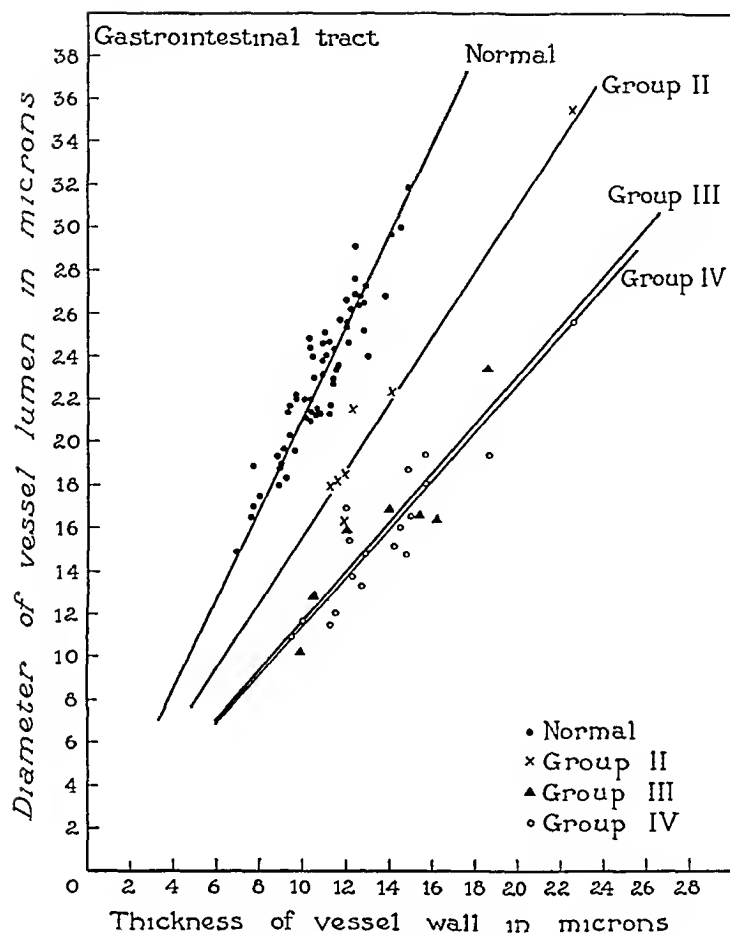


Fig 4—Ratio of the thickness of the wall to the diameter of the lumen in the arterioles of the gastrointestinal tract

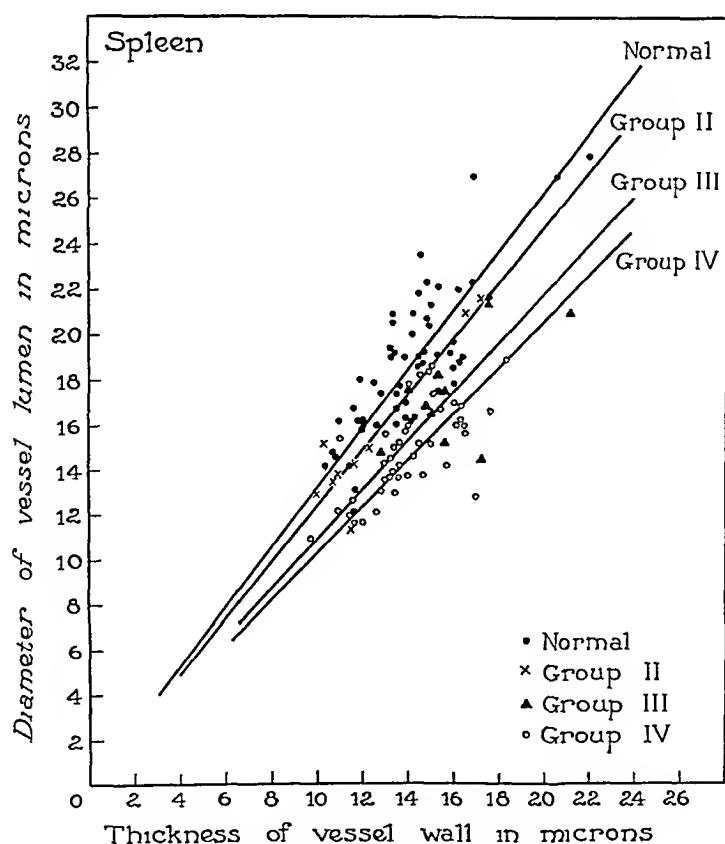


Fig 5—Ratio of the thickness of the wall to the diameter of the lumen in the arterioles of the spleen

Degenerative changes have been emphasized by Jores,<sup>20</sup> Fishberg,<sup>21</sup> Cain<sup>22</sup> and more recently Andrus. Substantiation of Johnson's original thesis has been offered by Jores in some cases, Fahr,<sup>23</sup> Brogsitter,<sup>24</sup> Kernohan and his co-workers, Moritz and Oldt and others. Moritz and Oldt made out three principal types of chronic disease of the arterioles. They expressed the belief that the hyalinized intima which they observed was the arteriolar counterpart of simple arteriosclerosis and that it was essentially a degenerative change. They regarded hypertrophy and degeneration of the media as changes incident to stretching of the vessel, and they noted hypertrophy of the media with greater frequency in hypertensive than in nonhypertensive persons. They also noted hyperplasia of the endothelium, which when it occurred in hypertensive patients was interpreted as representative of primary vascular inflammation or of an accelerated form of arteriolar sclerosis.

In my study thickening of the wall of the vessel was one of the conditions most constantly observed and was present in all groups of hypertensive patients. Vessels of equal caliber were not affected equally, but all showed some degree of change, this was true for the pancreas, liver, gastrointestinal tract and spleen. Thickening of the wall accompanied less severe degrees of hypertension (group 2) as well as the more severe forms. The histologic change which occurred in the arterioles of the patients in group 2 was apparently an increase in the muscular elements of the media, with thickening of the intimal and sub-intimal laminae.

Changes in the arterioles of the hypertensive patients of groups 3 and 4 were practically indistinguishable, except that in the latter group the changes were somewhat more profound than those in the other groups. The arterioles were affected essentially in the same way in the different tissues, although the pancreas seemed to suffer most severely. The changes in the arterioles of the spleen were not remarkable, as this tissue suffered rather severe arteriosclerotic changes normally, although mensuration revealed uniform but slight thickening of the wall. The liver and gastrointestinal tract were affected equally.

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20 Jores, L. Ueber die Arteriosklerose der kleinen Organarterien und ihre Beziehungen zur Nephritis, *Virchows Arch f path Anat* **178**:367-406, 1904.

21 Fishberg, A. M. Anatomic Findings in Essential Hypertension, *Arch Int Med* **35**: 650-668 (May) 1925.

22 Cain, E. F. Malignant Hypertension. The Histologic Changes in the Kidneys, *Arch Int Med* **53**: 832-850 (June) 1934.

23 Fahr, T. Ueber die Beziehungen von Arteriolsklerose, Hypertonie und Herzhypertrophie, *Virchows Arch f path Anat* **239**: 41-63, 1922.

24 Brogsitter, A. M. Zur Anatomie der Splanchnikusgefäße beim Hochdruck, *München med Wchnschr* **2**: 1049-1051 (Aug 1) 1924.



In the pancreas (fig 6 *A*) there was increase in the muscular elements of the media of the less severely involved arteriole, and there was thickening of this layer. There was also thickening of the intimal, subintimal and the adventitial layers. Sometimes there was associated replacement of the media by fibrous tissue. The internal elastic lamina

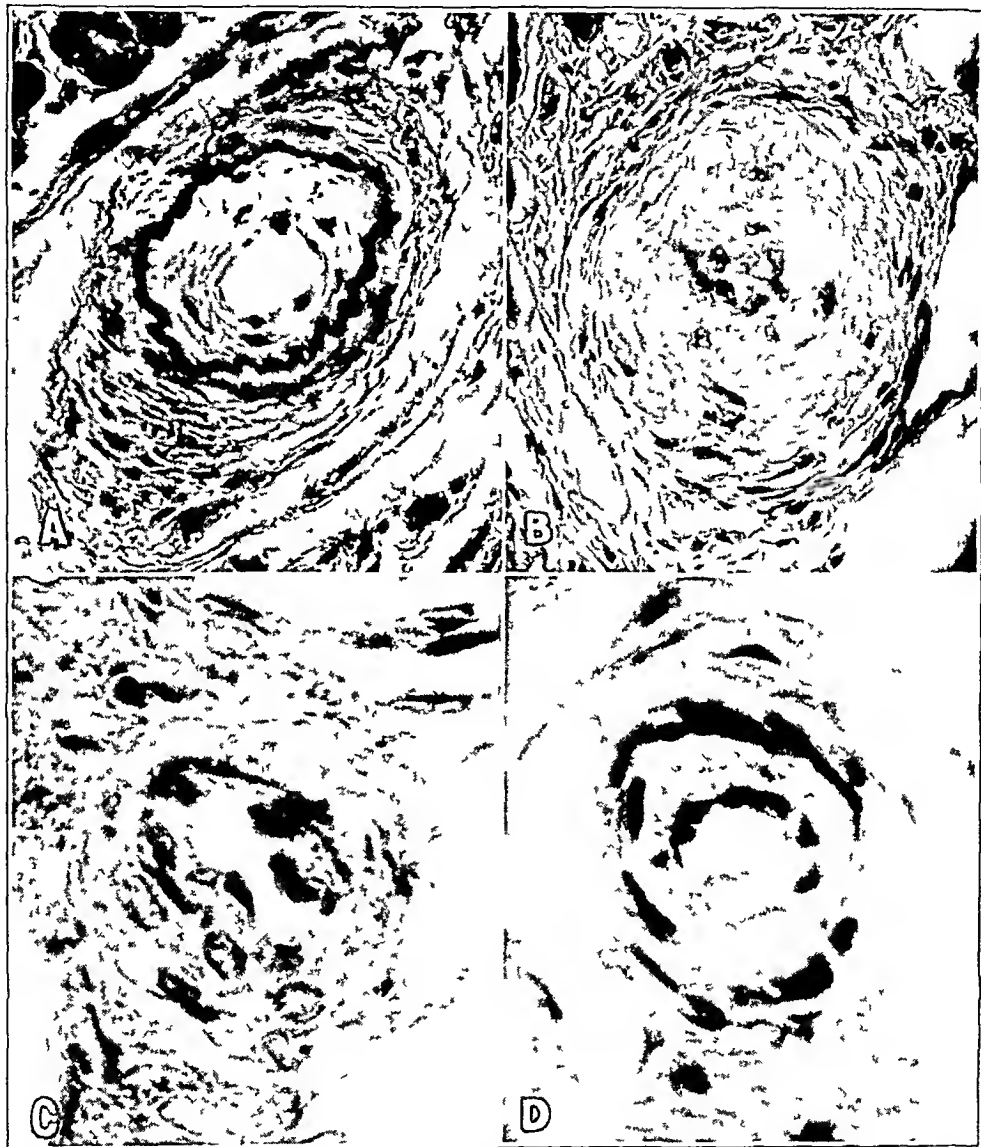


Fig 6—Photomicrographs of arterioles of a hypertensive patient of group 4. *A*, an arteriole of the pancreas, showing the thickened elastic lamina and the necrosis of the subintimal layer. The outside diameter of the arteriole is 100 microns (elastin H stain,  $\times 320$ ). *B*, an arteriole of the pancreas, showing the extreme thickening of the wall and the obliteration of the lumen. The outside diameter of the arteriole is 100 microns (hematoxylin-eosin stain,  $\times 350$ ). *C*, an arteriole of the liver, showing the thickened wall and the hyperplasia of the cellular elements of the media and the intima. The outside diameter of the arteriole is 45 microns (elastin H stain,  $\times 825$ ). *D*, an arteriole of the stomach, showing the increase of endothelial cells of the intima and the fibrosis of the media. The outside diameter of the arteriole is 90 microns (Van Gieson stain,  $\times 325$ ).

was hypertrophied and split in many cases. The greatest degenerative changes occurred in vessels in which marked thickening of the wall had occurred (fig 6 *B*). In these most of the increase in thickness of the wall was caused by proliferation and hyalinization of the intima. In many vessels the change went on to complete closure of the lumen, with resultant infarction and necrosis of the portion of tissue supplied.

Figure 6 *C* is representative of arteriolar changes observed in the liver. The increased thickness of the wall and the reduction of the diameter of the lumen are evident. The change in these vessels was predominantly hyperplasia of the nuclear elements of both the media and the intima. There was fibrosis of the adventitia and some replacement of the media by fibrous tissue, but in these cases hyperplasia of the intima and subintima leading to occlusion of the lumen was seen infrequently.

The arteriolar changes in the gastrointestinal tract (fig 6 *D*) closely resembled those noted in the liver. Thickening of the wall was subservient primarily to hyperplasia of the nuclear elements in the intima and media, with superimposed fibrosis, which was lamellated in some instances and homogeneous and hyaline in others.

#### COMMENT

Examination of arterioles of the pancreas, liver, spleen and gastrointestinal tract of the normal person gave no evidence of measurable change in the walls due to age. Marked measurable thickening of the arteriolar wall and reduction of the ratio of wall to lumen as compared with the normal ratio were noted in hypertensive patients of all ages. Thickening of the wall and the reduction of the ratio of wall to lumen were greater among those with more severe hypertension.

Arteriolar measurements lend justification to the clinical grouping of hypertensive patients. It is apparent that the more severely hypertensive patients of groups 3 and 4 exhibit anatomic changes in the arterioles which are closely parallel and more closely related to each other than they are to the changes of less severity that are typical of the arterioles of the hypertensive patients of group 2.

Of the four types of tissue studied, the pancreas gave evidence of the most pronounced changes in the arterioles when considered purely from the histologic standpoint, but when these changes were evaluated in the light of measurable factors it appeared that, as a tissue, the pancreas did not suffer changes in the arterioles to a significantly greater degree than did the liver or the gastrointestinal tract. All arterioles of equal size in these four organs were not affected equally, but when compared with normal ones all showed some degree of change.

Hyperplasia of the nuclear elements of the media appeared to be one of the earlier changes. Degeneration and fibrosis appeared to be later changes. If these observations are compared with those of Cain, of Kernohan and his co-workers and of Moritz and Oldt, the close analogy is striking. Kernohan stressed hypertrophy of the media in the arteriole of voluntary muscle of hypertensive patients. Certainly hypertrophy of the media has played a part in the changes in the vessels of the hypertensive patients of my series. Degenerative changes in the intima are prominent, however, in the more severely damaged vessels and comprise the greater part of the extremely thickened wall.

Considering the evidence compiled by previous workers, the changes that I have observed appear to substantiate the hypothesis that one of the significant and consistently seen conditions among hypertensive patients is generalized alteration of the arteriolar system, of uniform character and degree in different organs but varying in degree in proportion to the severity of the disease. Odel,<sup>25</sup> in a study of the myocardium, demonstrated that even in this tissue, which heretofore has been considered immune to arteriolar change associated with hypertension, there is consistent alteration of the arteriole in cases of severe hypertension. He indicated however, that the changes were much less pronounced than those which I have noted.

Why these changes in the vessels occur and what their true relation to hypertension is has not been explained. Whether they represent hypertrophy caused by increased work secondary to hypertension, as Johnson first postulated, or whether they are primary and by their presence can cause increased peripheral resistance, thus producing hypertension, is not known. However, from the evidence of previous studies and the results of this investigation it seems justifiable to conclude that generalized changes in arterioles occur in association with hypertension, that these changes are anatomic and that they are recognizable by virtue of measurable factors and of comparative standards, as demonstrated by histologic methods.

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25 Odel, H. M. Personal communication to the author.

# EPINEPHRINE IN OIL

A NEW, SLOWLY ABSORBED EPINEPHRINE PREPARATION

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Interest in compounds that produce a rise in blood pressure was aroused by Oliver and Schafer<sup>1</sup> in 1894, when they found that extracts of the adrenal gland when injected intravenously into animals produced a rise in blood pressure. Intensive study of the gland was begun by Abel,<sup>2</sup> von Furth<sup>3</sup> and Takamine.<sup>4</sup> It remained for Aldrich<sup>5</sup> to demonstrate the true formula for epinephrine, although the value of Abel's contributions is well recognized by the scientific world and it is he who is generally accorded the credit for the first isolation of the principle. This principle he named "epinephrin," while von Furth and Takamine, respectively, suggested the names "suprarenine" and "adrenalin."

Since the isolation of epinephrine, investigators have attempted to produce more active compounds with more prolonged effectiveness by modifying the structure of the molecule. Although a few changes have resulted in more active preparations, these, in turn, have been found too toxic for clinical use, while the compounds with longer effectiveness do not possess the activity of epinephrine.

The speed and duration of absorption of any compound which is injected subcutaneously or intramuscularly depend chiefly on the solu-

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From the Protein Clinic, Department of Medicine, and the Department of Pediatrics, Johns Hopkins Medical School and Hospital.

1 Oliver, G., and Schafer, E. A. On the Physiologic Action of Extract of the Suprarenal Glands, *J. Physiol.* **16** 1P, 1894.

2 Abel, J. J., and Crawford, A. G. On the Blood-Pressure-Raising Constituent of the Suprarenal Capsule, *Bull. Johns Hopkins Hosp.* **8** 151, 1897. Abel, J. J. Further Observations on the Chemical Nature of the Active Principle of the Suprarenal Capsule, *ibid.* **9** 215, 1898.

3 von Furth, O. Neuere Untersuchungen über die chemische Zusammensetzung der gefassverengernden Substanz in den Nebennieren, *Biochem. Centralbl.* **2** 1, 1903.

4 Takamine, J. The Blood-Pressure Raising Principle of the Suprarenal Gland, *J. A. M. A.* **38** 153 (Jan. 18) 1902.

5 Aldrich, T. B. A Preliminary Report on the Active Principle of the Suprarenal Gland, *Am. J. Physiol.* **5** 457, 1901.

bility of the original compound, on the absorbing area, which is dependent on the spreading of the injected substance in the tissues, and on the dosage. Watery solutions are rapidly absorbed because they spread as soon as injected, thereby forming a large surface for contact with the tissues. The diffusion of oily suspensions through the tissues is hindered by the film of oil. The oil also prolongs absorption by restricting the contact of the compound with the tissues (Sollmann<sup>6</sup>).

A suspension of epinephrine in oil, according to these theories, should be more slowly absorbed than the watery and commonly used solution of epinephrine hydrochloride. Recently, one of us (E. L. K<sup>7</sup>) briefly reported on the prolonged effectiveness of such a suspension. Strauch<sup>8</sup> had previously attempted to delay the absorption of epinephrine and other drugs by preparing emulsions of these substances, but no attempt had ever been made, prior to that reported by one of us,<sup>7</sup> to prepare a suspension of the powdered epinephrine base in a vegetable oil.

Although many compounds in vegetable oils are injected subcutaneously and intramuscularly, little is known of what actually happens to the oil itself. Binet<sup>9</sup> studied the absorption of olive oil injected subcutaneously into rabbits and has shown that the oil spreads through the subcutaneous tissues and finally reaches the interstices of the muscles. The oil is divided into droplets, which, in turn, become encysted, and the walls of these cysts soon become infiltrated with mononuclear cells, which digest the oil. The chemical changes, he stated, point to saponification, with liberation of the fatty acids. The same author has shown that the absorption of substances in combination with the oil is rapid in comparison with that of the oil, which may remain *in situ* for months. Schick and his co-workers<sup>10</sup> injected 2,250 Gm of olive oil subcutaneously into an 11 year old patient over a period of forty-one days and observed only a few remaining areas of swelling.

Dr. Carl G. Hartman, of the Carnegie Institute, made it possible for us to observe 4 monkeys which for many months had received subcutaneous injections of progynon (a solution of estrogen containing

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6 Sollmann, T. A Manual of Pharmacology, ed. 5, Philadelphia, W. B. Saunders Company, 1936.

7 Keeney, E. L. A Slowly Absorbed Epinephrine Preparation. Preliminary Report, *Bull. Johns Hopkins Hosp.* **62**: 227, 1938.

8 Strauch, C. B. Repository Injections. How To Obtain Lasting Effects with Injected Water-Soluble Medicaments Such as Insulin and Epinephrine, *J. A. M. A.* **92**: 1177 (April 6) 1929.

9 Binet, L. Absorption of Oil Injected Subcutaneously, *Bull. et mém. Soc. méd. d'hôp. de Paris* **49**: 1458, 1925.

10 Schick, B., Fries, M., Kohn, J., and Cohen, P. Observations of the Nutritional Effect of Subcutaneous Oil Injections, *Proc. Soc. Exper. Biol. & Med.* **21**: 445, 1924.

estrone [theelin] and some other substances) in corn oil. Four small subcutaneous nodules were palpated in the monkey that had received one hundred and thirty-one injections of 0.14 cc of the oil. No nodules could be felt in the 3 other monkeys, that had received one hundred and thirty-five, sixty-five and thirty injections, respectively.

Although there is no experimental work on record which endorses one vegetable oil over another as a vehicle for an injectant, peanut oil and olive oil are more commonly used than other types. Of these two oils, the former is considered to be less irritating because it generally contains fewer excess fatty acids. For this reason we have used peanut oil in preparing suspensions of epinephrine in oil. The method of preparing and administering this form of epinephrine, although it was briefly described previously,<sup>7</sup> will be included here in detail.

#### METHOD OF PREPARATION AND ADMINISTRATION

The peanut oil is first washed in a separatory funnel with 97 per cent alcohol in order to remove excess fatty acids. The washing is repeated until the supernatant alcohol becomes colorless. Two hundred cubic centimeters of oil is washed with approximately 100 cc of alcohol. The oil is then sterilized by means of dry heat.

Twenty cubic centimeters of the sterile oil is placed in a 30 cc dry-sterilized vaccine bottle, and to this is added 40 mg of finely powdered epinephrine base that has been weighed under as sterile conditions as possible. A rubber stopper, which has been sterilized in an autoclave, is inserted. The pipets used in transferring the oil to the vaccine bottles are dry sterilized. All precautions, therefore, are taken to prevent contamination with water and, in turn, oxidation of the epinephrine.

The powdered epinephrine is suspended in the oil as a result of vigorous shaking and then exposed to supersonic vibrations. The supersonic apparatus that we used had a vibration frequency of 350,000 per second. Frictional heat is evolved during the process of irradiation, and because of this the exposure is carried out in two stages of three and one-half minutes each, with an intervening ten minute period of cooling. The effect of the irradiation is to reduce the size of the original particles of epinephrine and to cover them thoroughly with a film of oil. Occluded air bubbles are also removed.

The formation of a suspension of this type is dependent on Stokes' law—the velocity of a following particle is in direct ratio to the diameter and the specific gravity of the particle, and the viscosity of the fluid through which it descends.

The powdered epinephrine was not sterilized before being added to the oil, and for this reason, aerobic and anaerobic cultures were made of the epinephrine in oil before any injections were given. The material was always found to be sterile.<sup>11</sup>

Dry-sterilized syringes and needles are used in administering the epinephrine in order to prevent contamination with water. Although the material is preferably given subcutaneously, intramuscular injections are made if the patient complains

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<sup>11</sup> Recently we found that epinephrine in oil can be sterilized by being placed in an autoclave for fifteen minutes at 15 pounds (6.8 Kg) of pressure. Although the heat changes the color of the epinephrine powder from white or buff to light tan, there is no appreciable change in the physiologic activity and clinical effectiveness of the preparation.

of great discomfort from the subcutaneous administration. Numerous consecutive intramuscular injections can be given without the slightest discomfort.

Sedimentation of the particles of epinephrine can be retarded by keeping the material in a refrigerator. Epinephrine in oil is not labile and should last indefinitely if contamination with water is prevented.

#### PLAN OF STUDY

Epinephrine in oil was administered to 4 patients with chronic bronchial asthma and 7 patients with chronic asthmatic bronchitis who had been taking regular daily injections or inhalations of epinephrine hydrochloride over periods ranging from three months to eight years. A decrease in the number of asthmatic attacks with less frequent administration of epinephrine in such cases indicated that the epinephrine in oil was slowly absorbed and that it possessed a prolonged effectiveness. The comparative effectiveness of epinephrine hydrochloride and epinephrine in oil was observed in 11 patients during one or more acute paroxysms of asthma. In a similar manner, observations were made on a patient with urticaria and another with serum sickness.

The hyperglycemic response to epinephrine in oil was observed in 5 patients, and the results were compared with those obtained after the administration of epinephrine hydrochloride to the same patients. The cardiovascular response to epinephrine in oil was noted in 3 cases. Although no observations were made by us on the cardiovascular response to epinephrine hydrochloride, sufficient data on the subject are available in the literature to allow us to make fairly accurate comparisons.

#### RESULTS AND REPORTS OF CASES

##### *Observations on patients with chronic bronchial asthma*

CASE 1 (chart 1) —Miss D. D., a 21 year old white woman, was known to have had asthma for the past ten years. She had been found hypersensitive to dust,orris, feathers and ragweed, for which she had been treated off and on for the past six years. For three months prior to treatment with epinephrine in oil she had had frequent recurring paroxysms of asthma, for which she administered to herself epinephrine hydrochloride subcutaneously. From October 29 to November 30 an accurate daily record was kept of the number of asthmatic seizures and the necessary injections of epinephrine hydrochloride. Treatment with epinephrine in oil was carried out at her home. The details and the results of such therapy during a nineteen day period of study are accurately depicted in chart 1. The epinephrine in oil was administered subcutaneously in the upper portion of the arm from November 30 to December 6. During this period she complained of soreness at the site of each injection and some redness, with swelling. Induration was noted. Therefore an attempt was made to reduce the quantity of oil injected by preparing a more concentrated suspension. Fifteen minutes after the administration of this suspension she experienced palpitation and nervousness, which lasted for forty-five minutes. No such symptoms had previously been noted. On December 7 the original suspension was reinstituted, but the injections were made intramuscularly in the buttock. There was no discomfort at the site of injection, and no untoward symptoms referable to the epinephrine followed. Thereafter all injections were made in this way. On December 15 she was given an injection of epinephrine in oil which had not been exposed to supersomic influence. On the following day an injection of the material which had been irradiated for seven minutes was given,

and the day after a specimen that had been irradiated for fourteen minutes was administered. There was no difference in the clinical effectiveness of the three preparations. The patient left Baltimore on December 18.

CASE 2 (chart 2)—J. D., a 30 year old white man, married, was known to have had asthma and hay fever for twenty years. He had been found hypersensitive to dust, orris and ragweed, for which he had been treated for the past four years. For three years he had not been able to sleep a night through because of asthma, attacks occurring regularly at 3 a. m. and again at 6 a. m. A nebulizer for epinephrine hydrochloride had been employed to provide relief. Because of the constant, regular occurrence of asthma, night after night, the patient was an unusually good subject on whom to test the prolonged effectiveness of epinephrine.

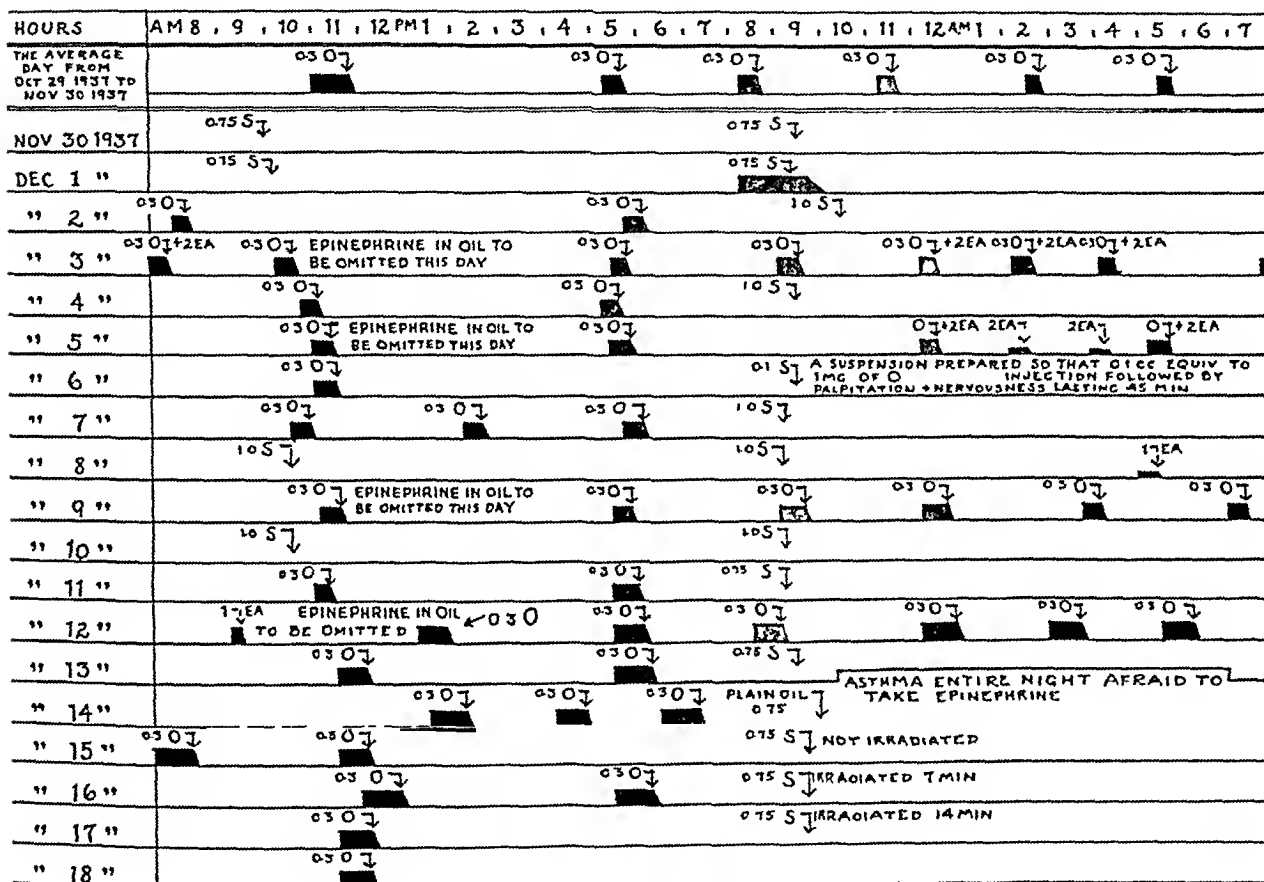


Chart 1—In charts 1 to 8, inclusive, the blackened areas represent attacks of asthma. The arrows indicate the administration of some preparation of epinephrine. O indicates "ordinary" epinephrine hydrochloride (in milligrams), S, slowly absorbed epinephrine in oil (in cubic centimeters), EA, capsules of ephedrine and amytal, and N, nebulized epinephrine hydrochloride (1:100). This chart gives the data for a woman aged 21 (case 1).

in oil. With 0.65 cc given at 7 p. m., he was able to sleep the night through, free from asthma (February 25). However, when the same dose was administered at 5 p. m. (February 18), the attack occurred as usual. It seemed, therefore, that this dose of epinephrine in this case was effective for eight hours but not for ten hours. All the treatments were given at the patient's home. The injections were made subcutaneously in the upper portion of the arm, and no discomfort at the site of injection was experienced. Larger doses might have been effective for



longer intervals, as in other cases, but because they produced headache, palpitation and nervousness we felt it inadvisable to subject him to this discomfort

CASE 3 (chart 3) —B B, a 35 year old white man, married, was known to have had asthma for the past two years. During this time he had spent sleepless nights because of persistent asthma, which was slightly ameliorated by the frequent and repeated use of a nebulizer containing epinephrine hydrochloride. Small injections of epinephrine hydrochloride were said to have made him nervous. During study of his case in the Johns Hopkins Hospital, all cutaneous tests gave negative reactions, but an infection in the paranasal sinuses was discovered. After an operation on the sinuses his symptoms were alleviated. Prior to the operation he was treated with epinephrine in oil, which gave him his first nights free from asthma in two years. All injections were made subcutaneously in the upper portion of the arm. He complained of slight soreness at the site of administration, which lasted only twenty-four hours, but there was no induration, swelling or redness.

CASE 4—Mrs R G, a 48 year old white woman, had complained of asthma for the past two years. During this period she had used a nebulizer containing epinephrine hydrochloride two or three times every night, thereby obtaining only temporary and partial relief from symptoms. For two weeks prior to the usage of epinephrine in oil the asthma had become worse, so that it was necessary for her to use the nebulizer three or four times every day and every night. At 5 45 p m on April 7, 1938, a mild attack of asthma occurred while she was at our office, and she was given 125 cc of epinephrine in oil. She experienced relief from her symptoms in forty-five to sixty minutes and remained free from asthma for the following twenty-four hours. This was her first night free from symptoms in two years. At 5 p m the following day she was given a similar injection, and again she slept a night free from asthma. With two injections of 125 cc of epinephrine in oil she had remained free from symptoms for forty-eight hours. Although her history suggested an inhalant type of bronchial asthma, sufficient studies had not been made to determine the exact nature of the allergy. The injections of epinephrine in oil were made subcutaneously in the upper portion of the arm. There was slight soreness at the site of each injection for the following forty-eight hours, but there was no swelling, induration or redness.

*Observations on patients with chronic asthmatic bronchitis*

CASE 5 (chart 4) —Miss B T, a 50 year old white woman, was known to have had asthmatic symptoms for the past ten years. She had had a complete study for allergy, with negative findings. A chronic sinus infection had been treated at various intervals by operative procedures, and after each operation she remained free from asthma for six to eight weeks. At the end of this period the previous symptoms would return with the usual severity. For the past three years she had resorted to frequent daily injections of epinephrine hydrochloride to obtain relief (chart 4). The asthma was generally so severe at night that she was forced to sit upright in bed. With one injection of epinephrine in oil at 8 p m, she was able to lie flat in bed and sleep most of the night, but it was generally necessary for her to have an injection of epinephrine hydrochloride about 3 a m. However, a few nights were spent entirely free from symptoms. With an injection of epinephrine in oil in the morning and one in the evening, she remained comfortable for twenty-four hours. With such a regimen it was necessary for her to have an additional injection of epinephrine hydrochloride, but never more than two a day. After the use of epinephrine in oil was stopped, the asthmatic attacks gradually reappeared, with the usual frequency and severity.

HOURS	8	9	10	11	12PM	1	2	3	4	5	6	7
FOR 3 YEARS ASTHMA DAILY BETWEEN 3AM AND 6AM												
DEC 10, 1937								S ↓ 1.00	Nervousness Palpitation for 1 hr.			
" 11-16 "	NO EPINEPHRINE IN OIL ADMINISTERED											
" 17 "								S ↓ 0.75	Nervousness for 45 minutes			
" 18-JAN 4	NO EPINEPHRINE IN OIL ADMINISTERED											
JAN 5, 1938								O ↓ 0.5 cc	Nervousness palpitation in 2 min for 30 minutes			
" 6-7 "	NO EPINEPHRINE IN OIL ADMINISTERED											
" 8 "								S ↓ 0.5				
" 9-FEB 3 "	NO EPINEPHRINE IN OIL ADMINISTERED											
FEB 4, "								S ↓ 0.75	90 later a little - Nervousness			
" 5-10 "	NO EPINEPHRINE IN OIL ADMINISTERED											
" 11 "								S ↓ 0.75	Slight nervousness			
" 12-17 "	NO EPINEPHRINE IN OIL ADMINISTERED ASTHMA WORSE											
" 18 "								S ↓ 0.65				
" 19-24 "	NO EPINEPHRINE IN OIL ADMINISTERED											
" 25 "								S ↓ 0.65				
" 26-27 "	NO EPINEPHRINE IN OIL ADMINISTERED											
" 28 "								S ↓ 0.65				

[illegible]

CASE 6 (chart 5) —R H, a 42 year old white man, married, was known to have had attacks of asthma for the past eighteen months. Eight months prior to his admission to the Johns Hopkins Hospital the attacks had become frequent and sleep had consisted of one to three hour naps between attacks. For relief from these attacks he had received frequent injections of some foreign epinephrine preparation. During his first twenty-four hours in the hospital the attacks of

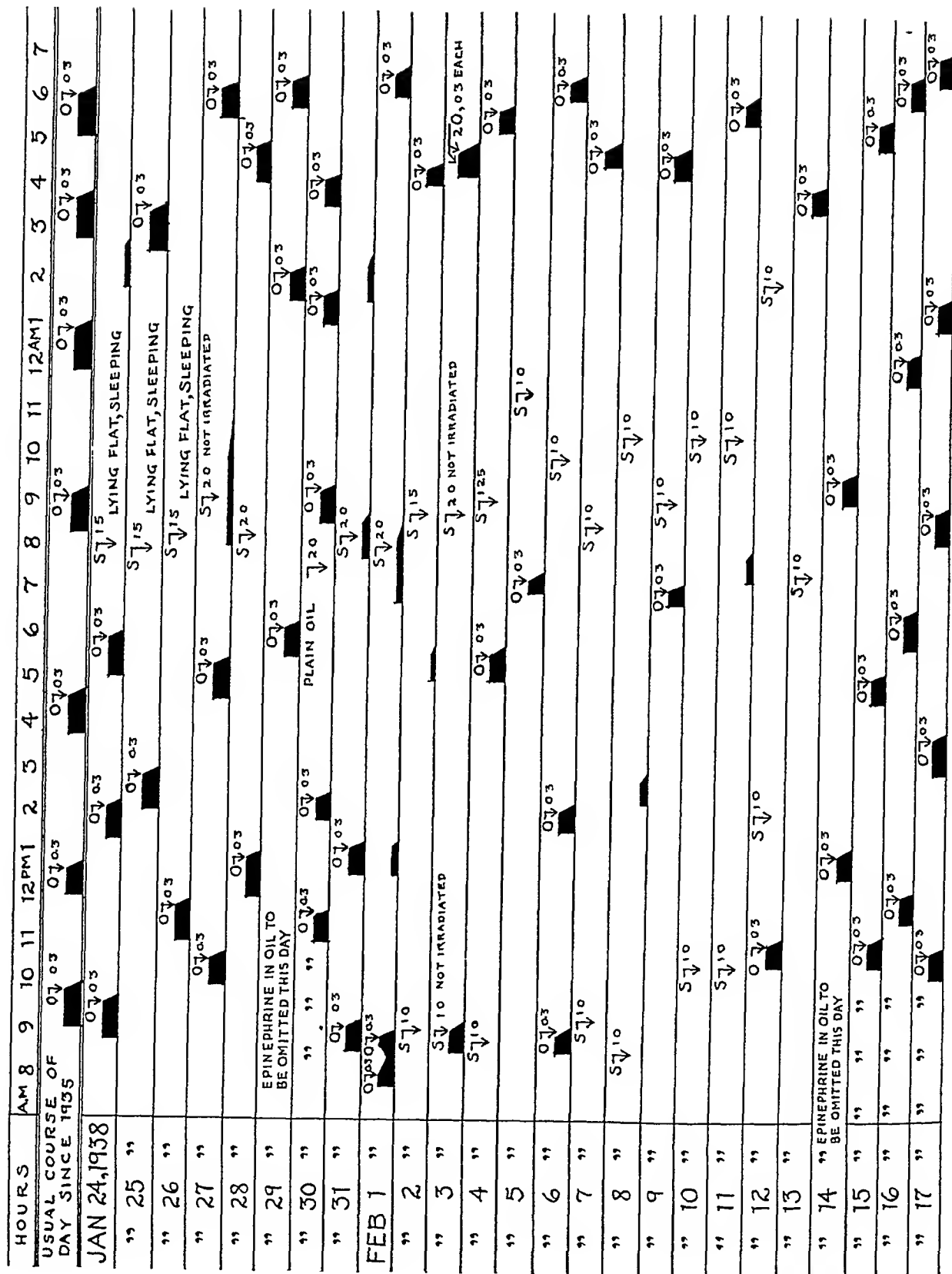


Chart 4 —Data for a woman aged 50 (case 5)

asthma were frequent and severe, but he insisted that this period represented his average day and night. He received gratifying relief from injections of epinephrine in oil, but it was not until large doses were administered (2 cc on January 5) that he had his first night entirely free from asthma. Even with such large doses there were no symptoms of nervousness or palpitation. A single subcutaneous injection of epinephrine in oil produced swelling, induration and redness, which lasted for forty-eight hours, while numerous and consecutive intramuscular injections resulted in only slight discomfort. During the course of diagnostic study, all tests for hypersensitivity gave negative results. A sinus infection was found, and an operation was performed on January 10. He remained free from asthma for the following six weeks, then his symptoms reappeared with equal severity, despite the fact that there was no recurrence of the sinus infection.

CASE 7 (chart 6) —S S, a 65 year old white man, married, was known to have had asthma for the past eighteen years. All cutaneous tests for hypersensitivity gave negative results. Ten years before entry, temporary relief for ten months

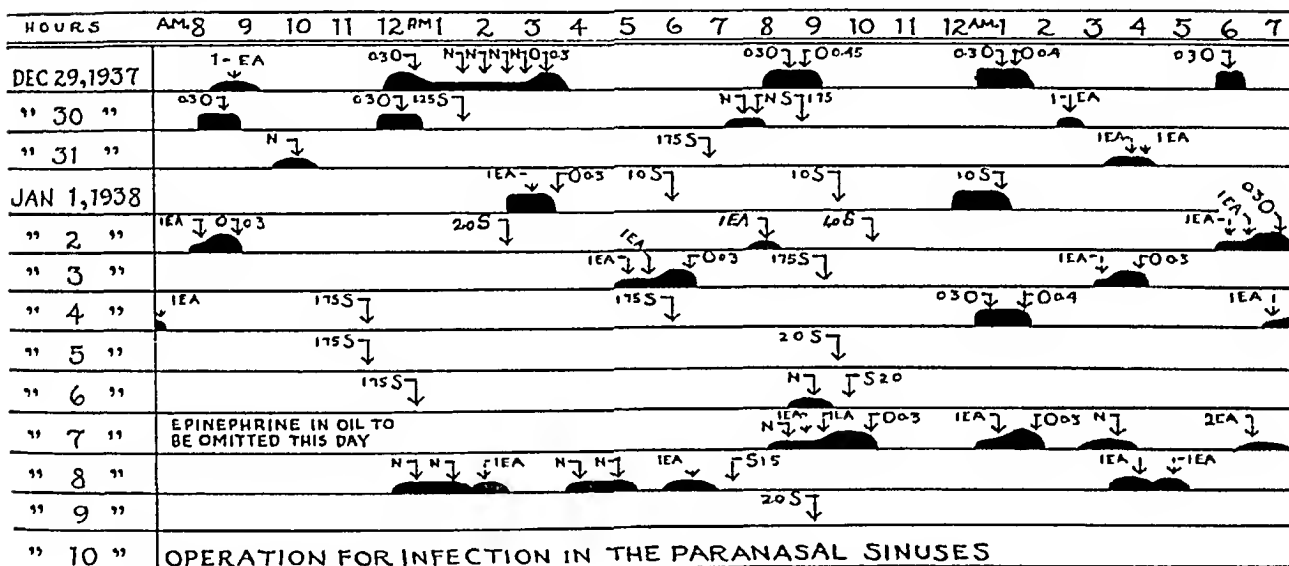


Chart 5—Data for a man aged 42 (case 6)

had followed a radical operation on the antrum. Since that time further nasal operative treatment was thought unnecessary, but his attacks of asthma had become more frequent. For the past eight years he had had an average of eight injections of epinephrine hydrochloride in twenty-four hours. With one injection of epinephrine in oil, he was able to go nine hours without asthma, but a night entirely free from symptoms was never obtained. During an unusually severe attack of asthma (January 28), when he had found it necessary to take hourly injections of epinephrine hydrochloride, the epinephrine in oil provided relief for four hours. All treatments were given at his home. The injections were made subcutaneously in the upper portion of the arm. Although there was slight soreness at the site of injection for twenty-four to thirty-six hours, swelling, redness and induration never occurred.

CASE 8 (chart 7) —D C, a 60 year old white physician, married, was admitted to the Johns Hopkins Hospital on Jan 25, 1938, because of asthma for the past eight years. All cutaneous tests for hypersensitivity gave negative results, various

nasal operations in the past had provided only temporary relief. For the past five years he had had an average of ten injections of epinephrine hydrochloride each twenty-four hours. On January 20 he was given 15 cc of epinephrine in oil intramuscularly in the buttocks. After the injection he remained without asthma for sixteen hours and experienced his first night free from symptoms in five years. However, five minutes after the injection he complained of nervousness, palpitation and irregular cardiac action, which lasted for sixty minutes. Because of the rapid appearance of these symptoms it was the impression that part of the material had entered a small blood vessel during the injection.

The patient was discharged from the hospital the following day and was given a supply of epinephrine in oil to administer to himself. Because of the unfortunate symptoms which followed the first injection that was given to him, he was advised to administer the material subcutaneously in small amounts and to increase the dose at his discretion. The data from which the chart was constructed were thus obtained from the patient and not by direct observation. He reported that mild redness and induration were noted at the site of injection for twenty-four to forty-eight hours.

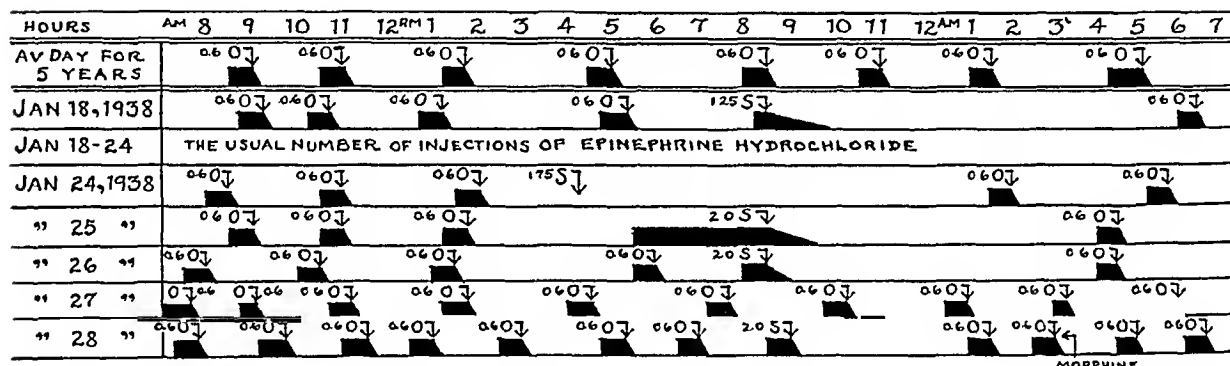


Chart 6—Data for a man aged 65 (case 7)

CASE 9 (chart 8)—J U, a 28 year old Negro, single, was known to have had asthma for the past three years. Cutaneous tests for hypersensitivity gave negative results. Exhaustive surgical treatment of the nose and throat had failed to provide more than temporary relief. The attacks, which generally followed an infection of the upper respiratory tract, were so severe and prolonged that frequent admissions to the hospital had been necessary. As a last hope, unilateral denervation of the right lung, with vagotomy on the left, had been performed, but the attacks continued to appear, with the same frequency and severity. It was during and between two periods of admission to the Johns Hopkins Hospital that the patient was treated with epinephrine in oil. Besides the apparently prolonged effectiveness of this preparation, it also gave relief when all other measures had failed. After his discharge from the hospital on January 20 he was followed for eight days at his home and received there one daily injection of epinephrine in oil. With this regimen he remained free from symptoms for five days. This he insisted was unusual, as it had always been necessary for him to use a nebulizer containing a solution of epinephrine hydrochloride many times during the night. On January 24 an infection of the upper respiratory tract developed and in four days he was again admitted to the hospital, with severe asthma. During the thirty-seven consecutive days of observation he received 66.5 cc of epinephrine in oil, all the injections

being made intramuscularly in the buttocks. He never complained of soreness at the site of administration, and there was never local redness, induration or swelling.

CASE 10—Miss G. P., a 45 year old white nurse, was known to have had asthma for the past thirty years. Cutaneous tests for hypersensitivity gave negative results. There was concomitant chronic sinusitis, which had been intensively treated, without any effect on the asthmatic state. During the many years of asthma there had developed marked chronic bronchitis. For the past eight years the asthmatic attacks had become frequent, and for relief she gave herself epinephrine hydrochloride. Although there was an adequate pathologic basis for her seizures, there was also a superimposed psychogenic factor. At first after the administration of epinephrine in oil she claimed to observe definite improvement. However, after an eighteen hour period without asthma, she experienced a severe attack, she felt that the severity was directly related to the unusually long period without

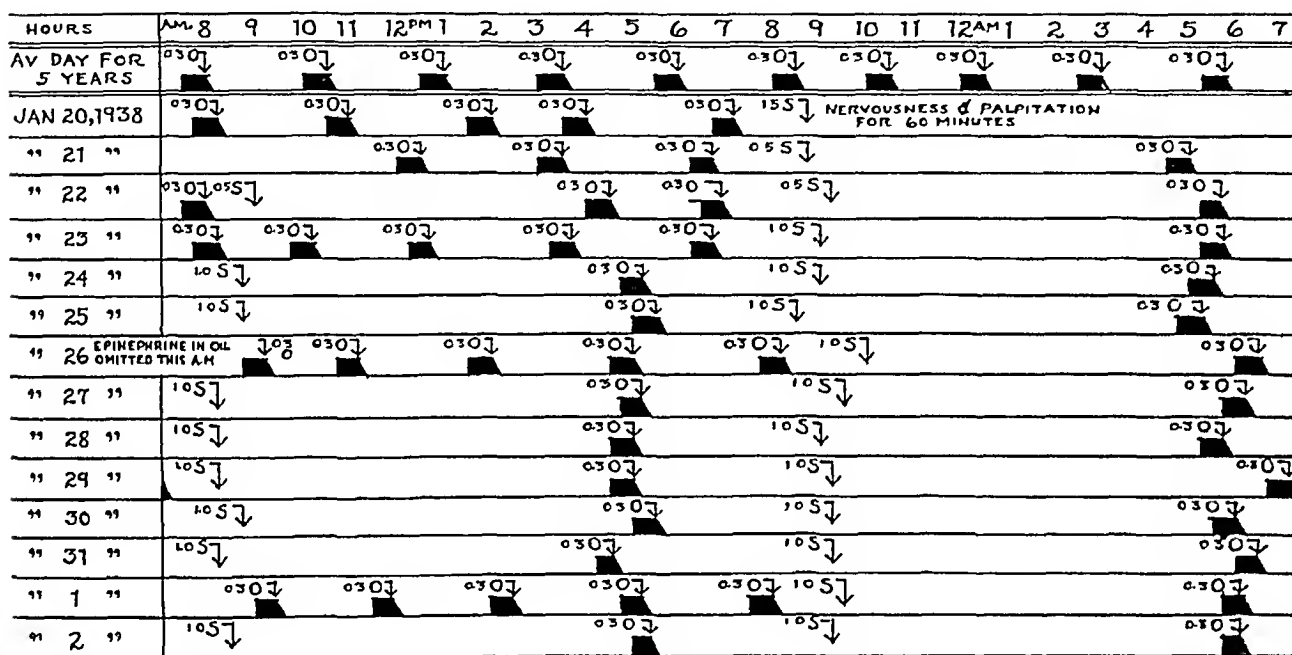


Chart 7—Data for a man aged 60 (case 8)

symptoms. She concluded that for her "frequent attacks of asthma were necessary to rid the bronchi of exudate." Thereafter, injections of epinephrine in oil failed to improve her state or prolong the interval between attacks. All administrations were made subcutaneously in the upper portion of the arm and were followed for twenty-four to forty-eight hours by some local swelling and induration.

CASE 11—C. J., a 30 year old Negro, married, was known to have had asthma for the past sixteen years. All cutaneous tests for hypersensitivity had shown negative results, and adequate surgical treatment of the nose and throat had failed to relieve the symptoms. For the past three years the attacks had been so frequent and severe that the patient had had an average of three to six injections of 0.5 to 1 mg. of epinephrine hydrochloride in twenty-four hours. With 12 cc. of epinephrine in oil, administered on five different occasions during visits to the outpatient department of the Johns Hopkins Hospital, he was able to have nine to twenty-four hours free from asthma depending on whether the asthma on the day of treatment was of marked or of average severity. On three occasions, during an

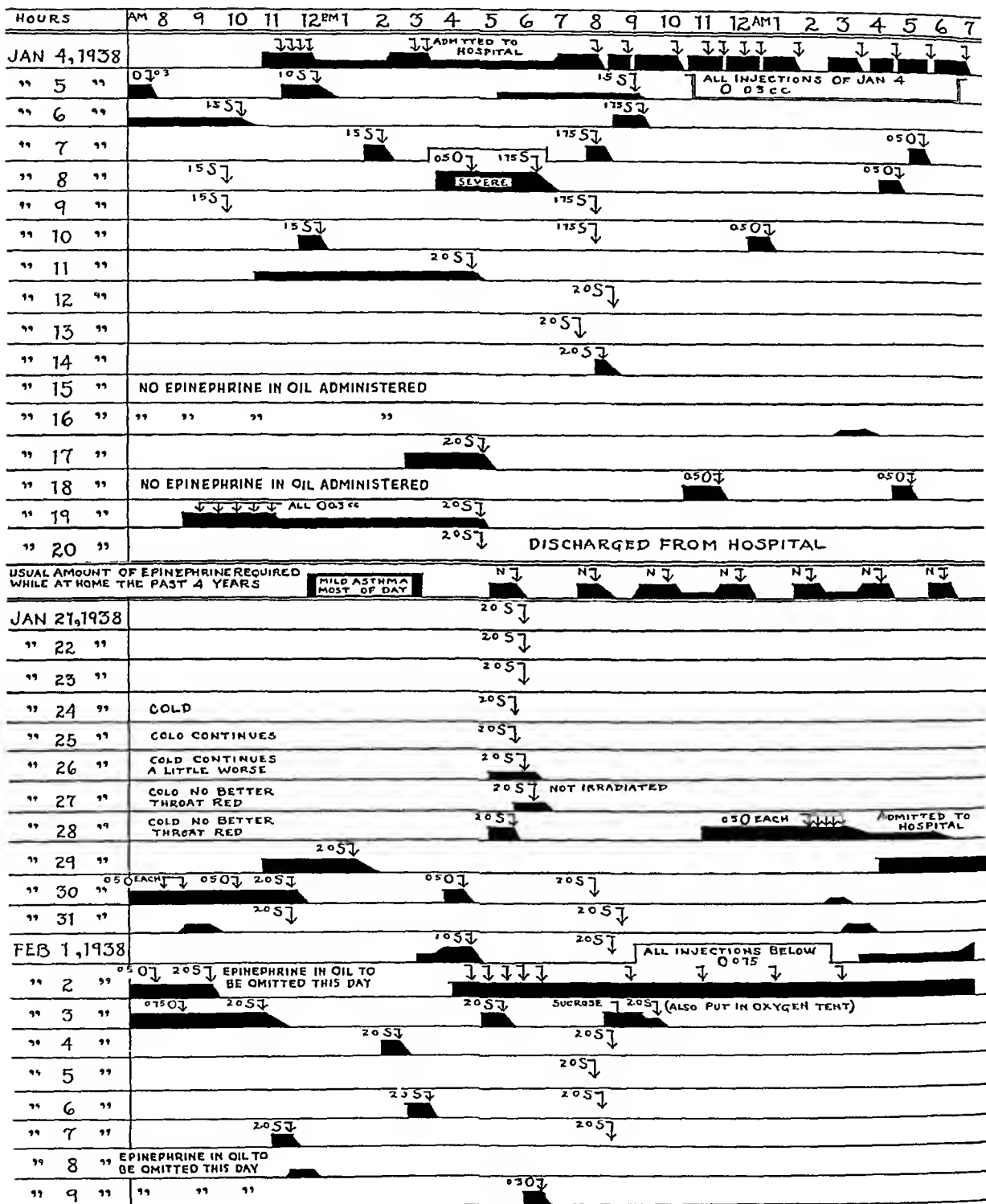


Chart 8—Data for a man aged 28 (case 9)

attack of asthma, 0.5 mg of epinephrine hydrochloride was administered prior to the epinephrine in oil to provide immediate relief. The injections of epinephrine in oil were made subcutaneously in the upper portion of the arm. There was never soreness, induration or swelling at the site of injection.

*Observations on patients during acute paroxysms of asthma (table 1)*

CASE 12—D. H., a 3 year old boy, was known to have had an extrinsic type of bronchial asthma, due to dust, for the past two years. The tonsils and adenoids were removed five months before entry. In the past three months the patient was

TABLE 1—*Summary of Observation on Eleven Patients with Acute Attacks of Asthma*

Patient, Age, Sex	Classification of Asthma	Duration of Asthma, Yr	Number of Attacks for Which Epinephrine in Oil Was Given	Amount of Epinephrine in Oil per Dose, Cc	Hours Free from Asthma After Treatment	Number of Attacks Aborted	Symptoms Referable to Epinephrine	Reaction at Site of Injection
D. H. 3, M	Extrinsic	2	3	0.65	10-16	1	None	None
D. B.* 3, M	Extrinsic	3½	2	0.70		2	None	Redness and induration for 24-48 hr
D. H. 6, M	Intrinsic	5½	1	0.50	10		None	None
A. H.* 46, F	Extrinsic	18	2	1.25	10	1	None	Slight sore ness for %6 hr
I. S. 25, F	? Psychogenic	3	1	1.00		1	None	None
E. D.* 25, F	Extrinsic	1	1	1.00	12		None	None
N. S.* 58, M	Intrinsic	19	5	1.50	12		None	Slight sore ness for 48 hr
L. H. 33, F	Intrinsic	¾	1	0.75	9-12		None	None
F. R.* 56, M	Intrinsic	5	7	1.50	9-12		None	Slight sore ness for 36 hr
E. C. 40, F	Extrinsic	10	4	0.75	12		None	None
H. H. 60, F	Intrinsic	10	4	1.00	12		None	Slight sore ness for 24-48 hr

\* Received 0.3 to 0.5 cc of solution of epinephrine hydrochloride prior to the injections of epinephrine in oil.

treated at home with epinephrine in oil on three different occasions because of asthma which followed exposure to dust in one instance and an acute infection of the upper respiratory tract in two other instances. The attack which followed exposure to dust was abated by one injection of epinephrine in oil, in the two other attacks there was relief of symptoms for ten to sixteen hours, respectively. Previously, during similar attacks, it had been necessary frequently to administer injections of epinephrine hydrochloride. There was no local reaction at the site of the injection of epinephrine in oil.

CASE 13—D. B., a 5 year old boy, was known to have had an extrinsic type of bronchial asthma, due to dust, for the past three and one half years. He was treated at home during two attacks with epinephrine in oil, with gradual but lasting



relief in each instance. One attack followed an infection of the upper respiratory tract, the other, excessive exertion. Previously, during similar attacks, he had been treated with frequent injections of epinephrine hydrochloride, which had given only temporary relief from symptoms. Definite redness, swelling and induration appeared at the site of injection of epinephrine in oil in about six hours and lasted for twenty-four to forty-eight hours.

CASE 14—D. H., a 6 year old boy, was known to have had attacks of asthma after infections of the upper respiratory tract for the past five and one-half years. Although there was definite hypersensitivity to dust, feathers and orris, these atopens apparently caused no symptoms. He was treated at home during one attack of asthma with 0.5 cc of epinephrine in oil, obtaining relief thereby for ten hours. Previously, in similar attacks, injections of epinephrine hydrochloride had given relief for only two to four hours. There was no local reaction at the site of the injection of epinephrine in oil.

CASE 15—Miss A. H., a 46 year old white woman, was known to have had seasonal asthma, due to grasses, for eighteen years. Treatment with specific extract for the past ten years had provided satisfactory relief, however, she did have an occasional extraseasonal attack of asthma, the cause of which was obscure. During two such attacks she was treated at home with epinephrine in oil. During one attack there was relief from symptoms for ten hours after one injection of epinephrine in oil, while during the other the asthma gradually disappeared, without a recurrence. Formerly, during similar attacks she had required frequent injections of epinephrine hydrochloride. The epinephrine in oil produced slight soreness at the site of administration, but neither redness nor induration developed.

CASE 16—Mrs. E. S., a 25 year old white woman, had had frequent attacks of intractable asthma prior to an operation for bilateral congenital cataracts. After the successful removal of the cataracts, with the establishment of good vision, the asthma entirely disappeared for three years. During the latter part of a recent pregnancy, asthma again reappeared. Exhaustive studies to reveal an allergic basis were unsuccessful. She was admitted to the Johns Hopkins Hospital with intractable asthma, and it was at this time that she received epinephrine in oil. Prior to its administration she had received four injections of 0.5 mg of epinephrine hydrochloride, each of which had given relief for two hours. After the injection of 1 cc of epinephrine in oil there was gradual relief of the symptoms in one hour, and she was able to sleep all night, free from asthma. The asthma did not recur, and she was discharged the following afternoon. There was no soreness, induration or redness at the site of the injection.

CASE 17—Mrs. E. D., a 25 year old white woman, was known to have had occasional attacks of asthma for the past year, following either an infection of the upper respiratory tract or exposure to dogs. During one of these attacks, the causation of which was related to both factors, she was given, at her home, 1 cc of epinephrine in oil, which provided relief from symptoms for twelve hours. Prior to its administration an injection of 0.5 mg of epinephrine hydrochloride had been effective for only two hours. The epinephrine in oil was administered subcutaneously in the gluteal region, without concomitant soreness, redness, induration or swelling.

CASE 18—N. S., a 58 year old white man, married, was known to have had asthma for the past nineteen years. Allergic studies indicated hypersensitivity to

dust, orris, feathers and summer and spring pollens. Studies of the nose and throat revealed an extensive sinus infection, for which he refused to be treated. The results of therapy with specific extract were therefore poor. The asthmatic attacks continued, and signs of chronic bronchitis developed. Ephedrine and nebulized epinephrine hydrochloride concomitantly lost their effectiveness. Injections of 0.3 to 0.5 mg of epinephrine hydrochloride provided relief from symptoms for one to three hours, while 1.5 cc of epinephrine in oil alleviated the asthma for twelve hours. During five attacks in the past two months the patient was treated at home with epinephrine in oil, in each instance a preliminary injection of epinephrine hydrochloride was administered to provide immediate relief. The injections of epinephrine in oil were administered subcutaneously into the upper portion of the arm. The patient complained of some soreness for twenty-four hours at the site of administration, but redness, induration and swelling never occurred.

CASE 19—Miss E. H., 35 years of age, was known to have had attacks of asthma for the past nine months, which appeared with striking regularity at 2 a. m. and again at 5 a. m. At the onset of these attacks she had usually taken one to three capsules of ephedrine, which provided satisfactory relief. Ephedrine at bedtime, however, failed to abort either of the morning attacks. During one of her visits to our office she received 0.75 cc of epinephrine in oil at 5 p. m. and thereafter remained free from asthma until 5 o'clock the following morning. The 2 a. m. attack had been aborted. Effectiveness with such a dose apparently was manifest for nine to twelve hours. It is unfortunate that further study of this patient was impossible. The injection of epinephrine in oil was made subcutaneously in the upper portion of the arm, without the occurrence of soreness, induration, swelling or redness. Subsequent diagnostic studies have failed to reveal the cause of her asthmatic symptoms.

CASE 20—F. R., a 56 year old white man, married, was known to have had asthma for the past five years. Cutaneous tests for hypersensitivity and studies of the nose and throat gave essentially negative results. Physical examination revealed chronic bronchitis. For the past three years the patient had used epinephrine hydrochloride in a nebulizer, usually with effectiveness, but occasionally he had more severe attacks, for which it was necessary to administer frequently injections of epinephrine hydrochloride. These injections gave only temporary relief, and the asthma usually reappeared in one or two hours. On seven occasions he was treated at his home during such an attack with epinephrine in oil. With 1.5 cc of epinephrine in oil and a preliminary injection of 0.5 mg of epinephrine hydrochloride, he was able to remain free from asthma for nine to twelve hours. All injections of epinephrine in oil were made subcutaneously in the upper portion of the arm. While there was slight soreness at the site of injection for twenty-four to thirty-six hours, redness, swelling and induration never occurred.

CASE 21—Mrs. E. C., a 40 year old white woman, was known to have had asthma for ten years. Nine years ago she had been found to be sensitive to dust, for which she had been specifically treated, with excellent results. One month ago, after moving into a new home, the asthma reappeared. The attacks usually came on after midnight and were so persistent that sleep was impossible. Three or four capsules of ephedrine, the dose being repeated at various intervals throughout the night, gave only temporary relief. With the injection of 0.75 cc of epinephrine in oil she was able to sleep all night, free from asthma. Such effectiveness was demonstrated on four different occasions. The treatments were administered at

the patient's home. All injections of epinephrine in oil were made subcutaneously in the upper portion of the arm, without concomitant soreness, redness, induration or swelling.

CASE 22—Mrs H H, aged 60, was known to have had asthma for the past ten years. Cutaneous tests for hypersensitivity gave negative results, and extensive treatment for chronic sinusitis had not caused any amelioration of the asthma. For the past four years the patient had had frequent daily and nocturnal attacks of asthma. Temporary relief from each attack had been obtained by an injection of 0.4 mg of epinephrine hydrochloride. With 1 cc of epinephrine in oil at 9 p m, the patient remained free from asthma for twelve hours and experienced her first complete night's rest in four years. A similar injection was given on three other occasions, with identical effectiveness. The treatments were given at the patient's home, and the injections were made subcutaneously in the gluteal region. Slight

TABLE 2—*Summary of Treatment Given Patient with Serum Sickness*

Date	Preparation	Relief of Symptoms	Onset of Relief After Medication, Minutes	Duration of Relief, Hr	Comment
2/25/38	Calcium lactate, 2 Gm	0	0	0	No effect
2/27/38	Epinephrine sulfate, 25 mg three times daily	?	?	?	No significant effect
3/ 2/38	Codeine sulfate, 64 mg	+++	15	4	Some relief from pruritus no effect on arthralgia
3/ 3/38	Codeine sulfate, 32 mg	+++	10	?	Slight relief of pruritus only
3/ 2/38	Epinephrine hydrochloride, 0.3 cc (1:1,000)	++++	5	1	Relief of pruritus and arthralgia, no change in character of urticaria
3/ 2/38	Epinephrine in oil, 0.75 cc	++++	30	12	Relief of pruritus and arthralgia no objective improvement of urticaria
3/ 3/38	Epinephrine in oil, 0.5 cc	++++	30	12	
3/ 4/38	Epinephrine in oil, 0.75 cc	++++	30	12	Temperature beginning to drop, urticaria disappearing

soreness at the site of injection persisted for about forty-eight hours, but redness, induration or swelling were never observed.

*Observations on patients with urticaria and serum sickness*

CASE 23 (chart 9)—Miss E M, aged 50, was seen two days after the development of generalized urticaria. A careful diagnostic study, which included tests for hypersensitivity, failed to reveal the cause of the condition. At the onset she received on two occasions an injection of 0.5 mg of epinephrine hydrochloride, which gave fleeting relief. With injections of epinephrine in oil she remained comfortable for ten to twelve hours or longer. The injections were given at her home and were made subcutaneously in the upper portion of the arm. Soreness, with redness, induration and swelling, followed each injection and lasted for about forty-eight hours.

CASE 24—Mrs E N, a 28 year old white woman, was admitted to the Johns Hopkins Hospital with acute lobar pneumonia due to *Pneumococcus* type VII. During the first twenty-four hours of her stay in the hospital she received 190,000 units of specific antipneumococcus serum. The temperature dropped, and in two days she was afebrile. She remained well until six days later, when generalized urticaria

and arthralgia appeared concomitantly with a rise in temperature. These symptoms were considered to be manifestations of serum sickness. For relief of the symptoms the patient was given, in seven days, calcium lactate, ephedrine, codeine sulfate, epinephrine hydrochloride and epinephrine in oil. The comparative effectiveness of each may be observed in table 2. The two preparations of epinephrine were the most effective in providing relief from symptoms, however, the epinephrine hydrochloride gave relief for only one hour, while the effectiveness of epinephrine in oil persisted for twelve hours. Although the subjective relief obtained with epinephrine preparations was marked, there was no objective improvement in the appearance of the urticaria. All injections of epinephrine in oil were made subcutaneously in the gluteal region. Soreness, induration and swelling never developed at the site of injection.

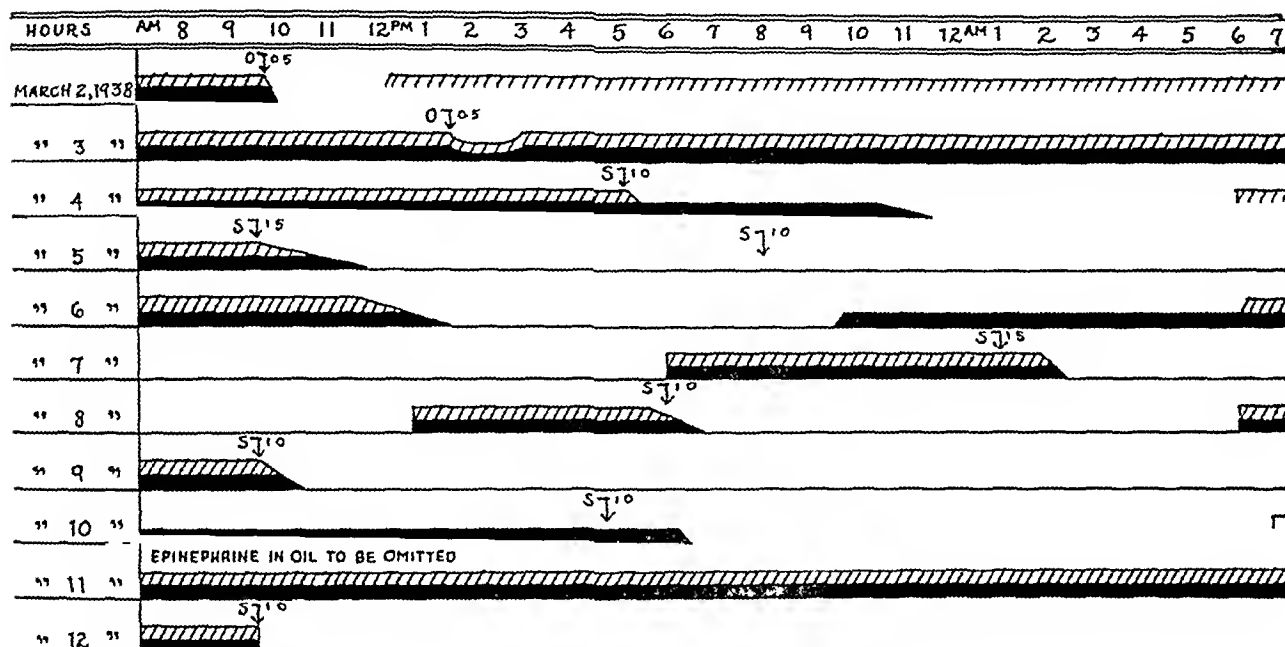


Chart 9—Data for a woman aged 50 (case 23). The hatched areas represent periods of subjective symptoms of pruritus. The solid black areas represent periods during which the patient had cutaneous manifestations of urticaria.

#### *Observations on the hyperglycemic response*

The experiments were performed on 5 subjects. Two patients (F and M) were healthy volunteers, and 3 (C, K and J) were convalescing from acute lobar pneumonia, in the medical ward of the Johns Hopkins Hospital. Each patient, having fasted for fourteen hours, was put at rest in bed in a quiet room, forty-five minutes later a specimen of blood was taken. Two of the patients (M and J) were then given subcutaneously 1 cc of epinephrine in oil and the 3 others (C, F and K) 1.5 cc. Specimens of blood were taken every fifteen minutes to two hours for eight or nine hours. All the determinations of the sugar content were made on capillary blood by the microscopic method described by Folin<sup>12</sup>. During the period of observation the patient was kept at rest in bed and was not allowed food, water or tobacco.

<sup>12</sup> Folin, O. Micro-Sugar Determination, *New England J. Med.* **206** 727, 1932.

The results of these experiments are graphically depicted in chart 10. It is seen that, with the exception of the curves for patients C and F, the configuration of the curves is not uniform. Three patients (C, F and K) received 15 cc of epinephrine in oil. In 2 cases (C and F) there was a gradual rise of the sugar content, which reached a maximum level after eight or nine hours, while in the third (K) the peak was reached in two hours, and approximately this level was maintained for the following seven hours. Two patients (M and J) received 1 cc of epinephrine in oil. In 1 case (M) the sugar content rose to its maximum level in two and one-half hours, was maintained at this level for the following two hours and then gradually fell in the ensuing two and one-half hours. In the other case (J) the sugar content rose to its peak in two hours and then gradually fell in the following six hours. In both of these cases the sugar content was above the fasting level at the end of eight hours.

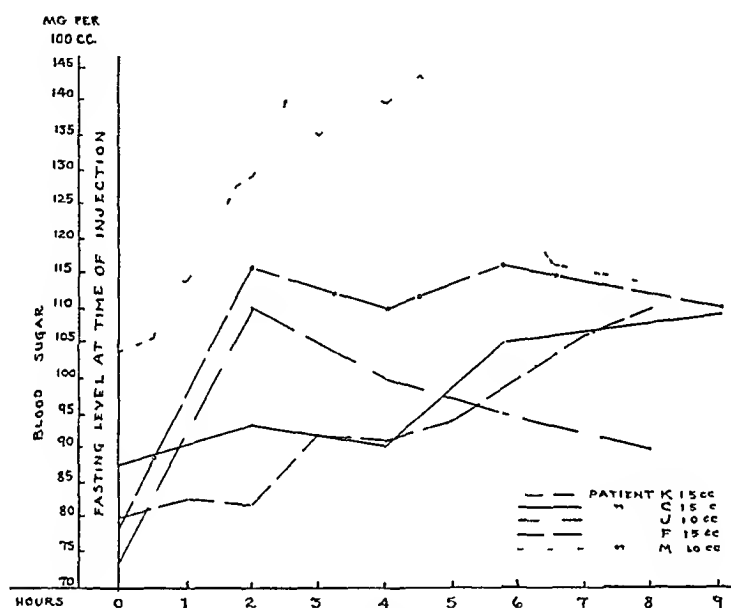


Chart 10—Curves showing the sugar content of the blood after an injection of epinephrine in oil

Two days later the same patients, under similar conditions, were given injections of epinephrine hydrochloride, and the response of the blood sugar was studied. Four patients (C, F, J and K) received 1 mg and the fifth patient (M) 0.5 mg. The curves thus obtained, as illustrated in chart 11, are strikingly different from those obtained after the administration of epinephrine in oil. After the injection of epinephrine hydrochloride there was a prompt rise in the sugar content (more marked than that obtained with epinephrine in oil), the maximum being reached in one or two hours, followed by rapid subsidence. The whole reaction was usually over in three hours. These results are in accord with the findings of Hamman and Hirschman<sup>13</sup> and Gjertz,<sup>14</sup> who likewise demonstrated that after an injection of

13 Hamman, L., and Hirschman, I. I. Studies on Blood Sugar, *Arch Int Med* 20: 761 (Nov) 1917

14 Gjertz, A. The Capillary-Venous Blood Sugar Difference in Adrenaline Tests, *Acta med Scandinav* 88: 464, 1936

epinephrine hydrochloride the sugar content of the blood rose to a peak in one or two hours and then rapidly fell to the fasting level during the following hour

*Observations on the cardiovascular response*

Clough<sup>15</sup> and Lyon<sup>16</sup> have demonstrated that there is a marked difference in the cardiovascular response of different persons to 1 mg of epinephrine hydrochloride. Generally, there is a fairly rapid rise in the systolic pressure to a maximum peak in five to twenty minutes. The amount of increase may range from 5 to 100 mm, but the majority of patients show a rise of 15 to 30 mm. The tachycardia and the fall in diastolic pressure may last longer than the rise in systolic pressure.

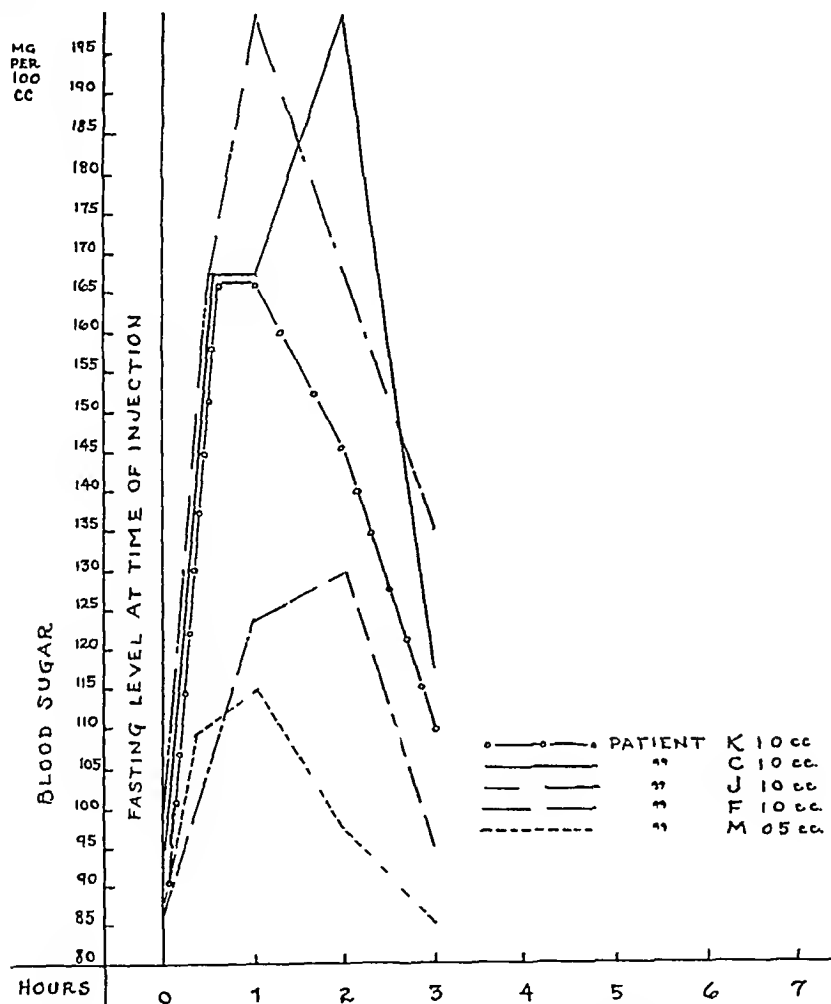


Chart 11—Curves showing the sugar content of the blood after an injection of a solution of epinephrine hydrochloride (1 1,000)

For further substantiation of the slow absorption and prolonged effectiveness of epinephrine in oil, it was necessary to compare the cardiovascular response with that already noted after the injection of epinephrine hydrochloride. Although such observations have been made in only 3 cases, it seemed desirable to record the data.

15 Clough, P. W. A Study of the Cardiovascular Reaction to Epinephrine, *Bull. Johns Hopkins Hosp.* **31**: 266, 1920.

16 Lyon, D. M. The Reaction to Adrenalin in Man, *Quart. J. Med.* **17**: 19, 1923.

The experiment was conducted on 3 patients (C, J and K) concomitant with the studies of the blood sugar. The method of preparing these patients for study has been described under the paragraph on the hyperglycemic response. The blood pressure and pulse rate were recorded at frequent intervals, and after forty-five minutes a constant level had been reached. After the injection of epinephrine in oil, further observations were made every fifteen to thirty minutes for eight or nine hours.

The blood pressure was determined with a sphygmomanometer by the auscultatory method. The diastolic pressure was read at the point at which there was an abrupt diminution in the intensity of the sound at the end of the third phase.

The pain and excitement associated with the injection and with the obtaining of specimens of blood caused a rise of 5 to 10 mm in the systolic pressure, which

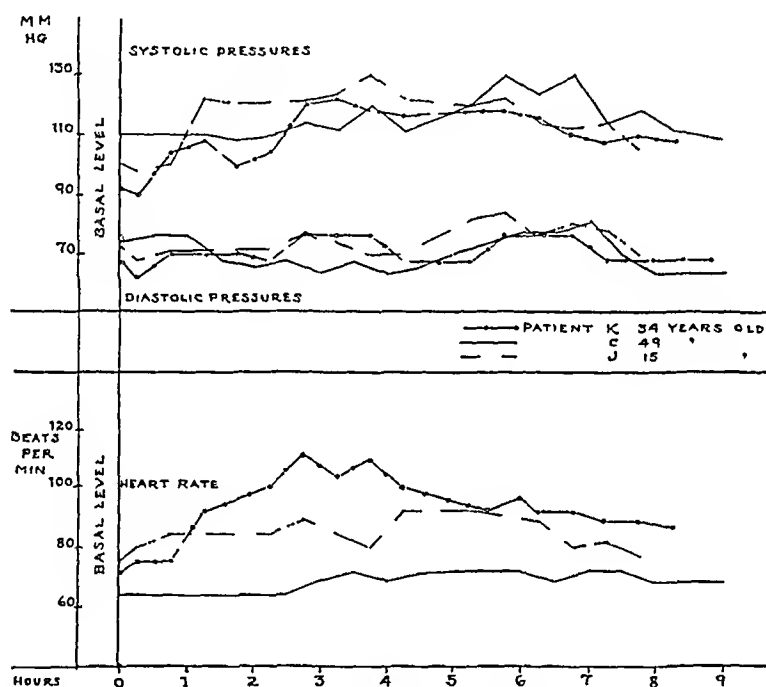


Chart 12—Curves showing the cardiovascular response obtained after an injection of epinephrine in oil

usually subsided after two minutes. Patients C and K received 15 cc and patient J, 1 cc of epinephrine in oil. The results are depicted in chart 11.

In 2 patients (J and K) the systolic pressure gradually reached its maximum level in three or four hours and then receded more gradually toward the basal level. The amount of increase in each case was 30 mm. In the third patient (C) an increase of 20 mm was reached in six hours and was followed by a recession to the basal level at the end of three more hours.

The readings for the diastolic pressure are difficult to interpret. In 2 patients (J and K) there was a gradual but fluctuating increase of 12 and 11 mm, respectively, which lingered behind the rise in systolic pressure but fell parallel with it. The third patient (C) showed a fall of 8 mm, followed by a return to the basal level, with a subsequent secondary fall. The pulse rate increased from 72 to 112 beats in patient K in two and one-half hours and gradually dropped in

the following six and one-half hours Patient J showed a gradual increase in the pulse rate from 76 to 92 beats in four hours, the rate receding to the basal level in the following four hours The rise in pulse rate of 8 beats in patient C is insignificant

#### COMMENT

With the dramatic introduction of protamine insulinate, there has been a revived interest among medical investigators in procuring delayed absorption of other drugs It is only natural that a portion of this enthusiasm should be directed toward epinephrine, the first and perhaps the most commonly used endocrine substance The minuteness and the lability of the epinephrine molecule offer a notable stumbling block in the achievement of such a goal, and it is because of this obstacle that we have designed to solve the problem in a different manner

Epinephrine is insoluble in oil, and for this reason the integrity of the molecule and its physiologic activity in such a vehicle should be unaltered For reasons that we have previously related, suspensions in oil are more slowly absorbed than watery solutions It is logical, then, to predict that a suspension of epinephrine in oil should be slowly absorbed and should exhibit its normal physiologic activity over a prolonged period

Finely powdered epinephrine is easily suspended in oil by being shaken, but better suspensions can be produced by exposing the material to supersonic radiation The influence of supersonic radiation is simply that of a superlative method of shaking, in that the apparatus emits vibrations at the rate of 350,000 per second Therefore, microscopic clumps of crystals are broken up, and occluded air bubbles are removed However, these microscopic differences in the character of the specimens before and after irradiation play no valuable role in their respective clinical effectiveness

There is little information in the literature pertaining to the absorption of oil injected subcutaneously or intramuscularly However, from purely clinical observations it is known that oil as an injectant is definitely irritating to some persons Although there is no scientific work on record which endorses one vegetable oil over another, peanut oil is generally considered to be less irritating than others This is most likely a conclusion derived from the comparative clinical trials of the various oily vehicles used in the preparations of bismuth and of estrogenic substances Therefore, because of these clinical deductions, we have used peanut oil in preparing the suspensions of epinephrine in oil

There is no report in the literature that peanut oil, acting as an atopen, has been the causative factor in the development of asthma However, it is not beyond the realm of possibility that allergic reactions to the oil will occur In 1 of our patients (D C) urticaria developed after epinephrine in oil was taken daily for six weeks However



there was also a concomitant flare-up of an old sinus infection, and we are still unable to say definitely that peanut oil was the exciting agent. Nevertheless, that was the only suspicious allergic reaction that we encountered, and we have given over two thousand injections of the material to allergic patients.

Patients with chronic asthma who had been taking regularly numerous daily injections or inhalations of epinephrine hydrochloride for months or years were ideal subjects on whom to test out the prolonged effectiveness of epinephrine in oil. Ten of these patients obtained relief from asthmatic symptoms for eight to sixteen hours with 0.65 to 2 cc doses of epinephrine in oil. Three patients received a morning and an evening injection and remained free from asthma for twenty-four hours. Only 1 patient failed to receive prolonged relief with adequate doses.

Although observations on patients with acute asthma cannot be so well controlled as those on patients with chronic asthma, a fair evaluation of the comparative effectiveness of epinephrine hydrochloride and epinephrine in oil could be made. Each of 11 patients was treated during one or more acute paroxysms of asthma with from 0.5 to 1.5 cc of epinephrine in oil and remained free from asthma for from nine to sixteen hours, but more generally for twelve hours. These results are remarkably gratifying when compared with those obtained during previous similar attacks, when frequent injections of epinephrine hydrochloride had been necessary and rest had been interfered with because of recurring paroxysms of asthma.

Observations were made on the comparative length of effectiveness of epinephrine hydrochloride and of epinephrine in oil in cases of urticaria and serum sickness and on the hyperglycemic response. The cardiovascular response to epinephrine in oil was compared with the data previously published on the cardiovascular response to epinephrine hydrochloride. The results obtained contribute more evidence in favor of the slow absorption and prolonged effectiveness of epinephrine in oil.

When treatment with epinephrine in oil is indicated, great care should be exercised in choosing the initial dose, for there is considerable individual variation in tolerance to epinephrine. For a patient with chronic asthma who has been taking frequent injections of epinephrine hydrochloride, it is safe to begin with 1 cc of epinephrine in oil. Subsequently the dose may be increased or decreased, depending on the patient's response. One patient may be made comfortable with 0.75 cc, while another may require 1.5 to 2 cc. During an acute attack of asthma the dose should be regulated according to the severity of the attack. As a general rule, 1 cc is sufficient in cases of moderately severe asthma. The immediate response to epinephrine in oil is more delayed than that to epinephrine hydrochloride, therefore, it is advisable during an acute attack to administer epinephrine hydrochloride prior to epi-

nephrine in oil The dose required for a child is naturally smaller than that for an adult, and its size, as for the adult, depends on the severity of the attack Usually, one half to two thirds of the dose for adults will be sufficient and safe The same cautious attitude should be adhered to in the management of patients with urticaria and serum sickness

Only 1 patient experienced severe untoward symptoms referable to the epinephrine After the administration of 1.5 cc this patient complained of violent palpitation and tachycardia for one hour However, because of the rapid onset of these symptoms, it was felt that a portion of the material had entered a small vessel during the injection It is as likely that the dose was too great, for subsequently he received many injections of 1 cc each without any ill effects

The injection of epinephrine in oil is preferably made subcutaneously in the upper portion of the arm or in the gluteal region There is usually slight or no discomfort at the site of injection after a single administration However, numerous consecutive injections are definitely irritating in some cases In these cases many intramuscular injections can be made without serious ensuing discomfort Although many injections of epinephrine in oil have been given, we have never observed the formation of subcutaneous nodules at the sites of injection

#### SUMMARY

Epinephrine in oil, a suspension of powdered epinephrine base in peanut oil, prepared so that 1 cc of oil contains 2 mg of epinephrine, is a preparation that is slowly absorbed

Ten patients with chronic asthma who had been taking frequent daily injections or inhalations of epinephrine hydrochloride received relief from asthmatic symptoms for from eight to sixteen hours with 0.65 to 2 cc doses of epinephrine in oil One patient received no prolonged effect from adequate doses

Eleven patients were treated during one or more acute paroxysms of asthma Each received from 0.5 to 1.5 cc of epinephrine in oil and remained free from asthma for nine to sixteen hours, but more generally for twelve hours

For 1 patient with urticaria and another with serum sickness epinephrine in oil provided relief from symptoms for twelve hours, whereas previously the effect from epinephrine hydrochloride had been fleeting

The hyperglycemic response to epinephrine in oil in 5 cases was maintained for at least eight or nine hours, while the response to epinephrine hydrochloride, though more marked, was usually over in three hours

The cardiovascular response to epinephrine in oil in 3 cases was maintained for eight or nine hours, while the response to epinephrine hydrochloride, as reported in the literature, is generally over in forty-five to ninety minutes.

The injections of epinephrine in oil are preferably made subcutaneously. There may or may not be slight discomfort at the site of a single administration, but consecutive injections are irritating in some cases. Numerous intramuscular injections can usually be made without following discomfort.

One patient experienced violent palpitation and tachycardia immediately after the administration of 1.5 cc of epinephrine in oil. Because of the rapid onset of these symptoms, it was felt that a portion of the material had entered a small vessel during the injection.

# PLASMA PROTEIN IN HEPATIC DISEASE

A STUDY OF THE COLLOID OSMOTIC PRESSURE OF BLOOD  
SERUM AND OF ASCITIC FLUID IN VARIOUS  
DISEASES OF THE LIVER

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Determination of the serum protein content is supposed to give a fairly accurate estimate of the colloid osmotic pressure of the blood serum. However, the frequent finding of normal levels for serum protein in the examination of patients with marked ascites and edema suggested that the usual protein determination is an inadequate measurement of the osmotic conditions at the capillary membrane and cannot be used to predict the effective osmotic pressure. It was found that measurement of the colloid osmotic pressure gave better knowledge of these physical processes and in many instances explained the presence of indeterminable edema and ascites.

Variations in the values for serum albumin and globulin in hepatic disease have been recognized for more than thirty years. Grenet<sup>1</sup> and Gilbert and Chiray<sup>2</sup> were among the first to note decrease in concentration of total protein among patients with cirrhosis of the liver, and their observation was later confirmed by Filinski,<sup>3</sup> Abram and Wallich<sup>4</sup>

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This work was done in the Division of Biochemistry of the Mayo Foundation and this paper represents part of the work for which the John Horsley Memorial Prize for 1938 was awarded to Dr Butt by the University of Virginia

1 Grenet, H. Diminution des albumines du serum sanguin chez les hepatiques, *Compt rend Soc de biol* **63** 552, 1907

2 Gilbert, A., and Chiray, M. Diminution des substances albumineuses du serum sanguin chez les cirrhotiques ascitiques, *Compt rend Soc de biol* **63** 487, 1907

3 Filinski, W. L'augmentation du taux de la globuline dans le serum du sang comme resultat de l'insuffisance hépatique, *Presse med* **20** 236, 1922

4 Abram, P., and Wallich, R. Modifications du serum sanguin au cours des cirrhoses du foie avec ascite. Inversion du rapport serines-globulines, *Compt rend Soc de biol* **101** 291, 1929

and others. More recently, Myers and Keefer<sup>5</sup> have made a study of 16 patients with cirrhosis of the liver, in all cases the total plasma protein value was decreased, particularly the albumin fraction. Similar but less extensive and less consistent alterations in the values for plasma protein were observed in 14 cases of other forms of disease of the liver. In larger groups of patients examined by Tumen and Bockus<sup>6</sup> and by Foley and others,<sup>7</sup> hypoalbuminemia was the most consistent alteration noted in the determination of serum protein. One of us (Dr Snell<sup>8</sup>) in a fairly large series of cases of hepatic disease noted, in addition to the alteration in the albumin-globulin ratio, the unusual rapidity with which changes in the total protein value and the albumin-globulin ratio can take place and intimated that for this reason repeated determinations of the serum protein content for the same patient might be necessary in order to be of some prognostic significance.

In addition to the quantitative change in the serum protein in hepatic disease, it long has been suspected that the mixtures of proteins which make up the so-called albumin and globulin fractions might also be altered in some of their physical or chemical properties. The recent immunologic study of the proteins in hepatic disease by Kendall<sup>9</sup> tends to confirm this assumption.

Most investigators feel that the decreased levels of serum protein in instances of hepatic injury probably result from failure of production of protein or protein-building substances in the liver, in addition to alteration in the equilibrium between the circulating and the stored protein. Some authors<sup>10</sup> have suggested that such variation in serum proteins may be of nutritional origin, others,<sup>11</sup> that defective formation

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5 Myers, W. K., and Keefer, C. S. Relation of Plasma Proteins to Ascites and Edema in Cirrhosis of the Liver, *Arch Int Med* **55** 349 (March) 1935.

6 Tumen, H., and Bockus, H. L. The Clinical Significance of Serum Proteins in Hepatic Diseases Compared with Other Liver Function Tests, *Am J M Sc* **193** 788, 1937.

7 Foley, E. F., Keeton, R. W., Kendrick, A. B., and Darling, D. Alterations of Serum Protein as an Index of Hepatic Failure, *Arch Int Med* **60** 64 (July) 1937.

8 Snell, A. M. The Effects of Chronic Disease of the Liver on the Composition and Physicochemical Properties of Blood. Changes in the Serum Proteins, Reduction in the Oxygen Saturation of the Arterial Blood, *Ann Int Med* **9** 690, 1935.

9 Kendall, F. E. Studies on Serum Proteins. I. Identification of a Single Serum Globulin by Immunological Means, Its Distribution in the Sera of Normal Individuals and of Patients with Cirrhosis of the Liver and with Chronic Glomerulonephritis, *J Clin Investigation* **16** 921, 1937.

10 Peters, J. P., and Eisenman, A. J. The Serum Proteins in Diseases Not Primarily Affecting the Cardiovascular System or Kidneys, *Am J M Sc* **186** 808, 1933.

11 Salvesen, H. A. Variations in the Plasma Proteins in Non-Renal Conditions, *Acta med Scandinav* **72** 133, 1929. Snell<sup>8</sup>.

of protein may be the primary factor, others, that there is a lack of reserve protein-building material normally stored in the liver,<sup>12</sup> and still others,<sup>5</sup> that the loss of albumin into the ascitic fluid or the increased capillary permeability, allowing escape of protein into the tissues,<sup>13</sup> may be the primary factor. In some recent unpublished studies we have been unable to demonstrate by means of a technic described by Landis and his associates<sup>14</sup> any excessive escape of protein into the peripheral tissues of patients with severe hepatic disease. There has been considerable debate over the correctness of these various hypotheses, and the critical review by Melnick and Cowgill<sup>15</sup> on the problem of hypoproteinemia only reemphasizes the lack of complete knowledge of this subject.

There are available few reports of studies in which the colloid osmotic pressure of the blood serum has been measured in hepatic disease.<sup>16</sup> Ivanov and Chervyakovskii<sup>17</sup> and Kellermann<sup>18</sup> reported markedly lowered values for colloid osmotic pressure for patients who had various diseases of the liver, decreased values for colloid osmotic pressure resulting from experimental hepatic damage to animals have

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12 Holman, R. L., Mahoney, E. B., and Whipple, G. H. Blood Plasma Protein Regeneration Controlled by Diet. I. Liver and Casein as Potent Diet Factors. *J. Exper. Med.* **59** 251, 1934. Kerr, W. J., Hurwitz, S. H., and Whipple, G. H. Regeneration of Blood Serum Proteins. III. Liver Injury Alone, Liver Injury and Plasma Depletion, the Eck Fistula Combined with Plasma Depletion, *Am. J. Physiol.* **47** 379, 1918.

13 Kaunitz, H. Serumweißkörper bei Leberkrankheiten, *Wien klin. Wchnschr.* **48** 1349, 1935.

14 Landis, E. M., Jonas, L., Angevine, M., and Erb, W. The Passage of Fluid and Protein Through the Human Capillary Wall During Venous Congestion, *J. Clin. Investigation* **11** 717, 1932.

15 Melnick, D., and Cowgill, G. R. The Problem of Hypoproteinemia, *Yale J. Biol. & Med.* **10** 49, 1937.

16 Yasuda, H. Studien über die blutweiß- und kolloid-osmoregulierende Tätigkeit der Leber. I. Ueber den Eiweißgehalt und den kolloid-osmotischen Druck des zu- und abstromenden Blutes der Leber, mit besonderer Berücksichtigung ihrer Veränderungen nach Eiweißverlust durch Aderlass und Plasmapheresis, Versuch an normalen Kaninchen, *Tohoku J. Exper. Med.* **31** 437, 1937, II. Ueber die Veränderungen des Eiweißes und des kolloid-osmotischen Drucks des zu- und abstromenden Blutes der Leber bei Nierenschädigung (Kantharidin- und Uranvergiftung), *ibid.* **31** 456, 1937, III. Ueber die Veränderungen des Eiweißes und des kolloid-osmotischen Drucks des Blutes in der Leber bei Leberschädigung, *ibid.* **31** 524, 1937, IV. Beeinflussung des Eiweißes und dessen kolloid-osmotischen Drucks des zu- und abstromenden Blutes der Leber durch vegetative Nervengifte, *ibid.* **31** 536, 1937.

17 Ivanov, L. P., and Chervyakovskii, N. I. Changes in the Albumin Fraction in Blood Serum in Liver Diseases, *Chem. Abstr.* **30** 6809, 1936.

18 Kellermann, V. Das Verhalten des kolloidosmotischen (onkotischen) Druckes im Verlaufe von Lebererkrankungen, *Ztschr. f. d. ges. exper. Med.* **100** 336, 1937.

been reported<sup>19</sup> Iversen<sup>20</sup> reported a single case of cirrhosis of the liver with ascites and edema in which the serum protein value was normal but the colloid osmotic pressure was reduced. In a few cases of cirrhosis of the liver, Butt and Keys<sup>21</sup> found the colloid osmotic pressure of the blood serum to be as low as a third of the normal value.

#### METHODS

The subjects examined were all patients observed at the Mayo Clinic. All the studies were made while the subjects were at rest in bed and fasting. Blood was drawn into a dry or oiled syringe from the antecubital vein. The ascitic fluid was removed in the usual manner with a trocar, collected in sterile containers and examined immediately.

The proteins in the serum were estimated by the standard Kjeldahl procedure, and the method of Howe<sup>22</sup> was used for separation of the albumin and globulin.

The colloid osmotic pressure of the blood serum was measured by a modification of the membrane bag arrangement of Starling,<sup>23</sup> Adair and Robinson,<sup>24</sup> Keys and Taylor<sup>25</sup> and others. The details of the method will be presented elsewhere, but a few essentials will be given here. The serum was diluted with an equal volume of a phosphate buffer solution at  $pH$  7.4, which is approximately isoionic and iso-osmotic with the serum. Small, fairly rigid collodion sacs were used which previously had been proved to be protein tight. The same buffer solution was used for the external medium, and the entire system was kept at 0 C. Usually equilibration was complete within forty-eight hours, but in all observations in the present series the osmometers were observed for some days longer. At the end of equilibration the nitrogen value of both the inner and the outer fluid was determined and compared with the protein and nonprotein nitrogen values of the original serum. The values for colloid osmotic pressure were corrected to the original concentration of the protein in the serum by means of standard curves for protein dilution<sup>26</sup>. All determinations were made in duplicate.

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20 Iversen, P. Untersuchungen über die Ascites-Pathogenese, *Klin. Wchnschr.* **7** 2001, 1928.

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24 Adair, G. S., and Robinson, M. E. The Analysis of the Osmotic Pressures of the Serum Proteins, and the Molecular Weights of Albumins and Globulins, *Biochem. J.* **24** 1864, 1930.

25 Keys, A., and Taylor, H. The Determination of the Colloidal Osmotic Pressure in Blood Serum and Similar Fluids, *J. Biol. Chem.* **109** 47, 1935.

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TABLE 1—*Atrophy of the Liver (Cirrhosis)*

Case	Sex	Age, Yr	Hemo- globin, Gm per 100 Cc		Erythro cytes, Millions per Cu Mm	Macrocytosis	Urine Albu min, Grade*	Edema, Grade*	Ascites, Grade*	Serum Bilirubin, Mg per 100 Cc†	Choles terol, Mg per 100 Cc	Urea, Mg per 100 Cc	Liver Function			Serum Protein, Gm per 100 Cc	Serum Albumin, Gm per 100 Cc	Albumin Globulin Ratio	Colloid Osmotic Pressure, Min of Water
													Benzole Acid, Gm Excreted as Hippuric Acid in 1 Hours	Brom- sul Excre tion, Grade*					
1	M	47	13.8	4.33			0	1	1	D 3.8	260	26		2		5.4	2.65	1.00	198
2	M	47	12.0	3.71		Generalized	1	3	1	D 3.0	136	30		3		6.7	1.36	0.45	200
3	M	45	12.1	3.01		Generalized	3	2	1	D 20.0		101				4.6		0.90	195
4	M	17	12.0	2.96		Marked	1	1	0	D 10.7	62	30	1.13			6.9	3.78	0.46	193
5	M	43	10.5	2.67		Generalized	1	2	1	D 7.5	287	16	2.89			6.9	0.88	0.71	207
6	M	52	14.1	1.50		Generalized	1	3	2	D 3.3	167	46	1.32	1		6.9	2.53	0.63	2.0
7	M	53	15.5	1.41		Slight	0	0	0	D 1.6		20				7.0			238
8	M	56	13.1	1.21			2	0	1	D 21.4	122	30	2.10			6.6	2.41	0.60	213
9	M	46	13.1	3.61		Marked	0	2	2	D 6.2	211	26	0.37			6.3	1.87	0.63	222
10	M	53	13.5	3.30		None	0	2	3	D 2.0		31				7.9	2.20	0.83	230
11	F	49	11.0	3.46		Marked	0	1	2	D 1.7	172	26		1		7.9	2.31	0.71	268
12	M	42	12.6	3.71		Generalized	0	1	3	D 5.7	163	21		3		6.0	1.70	0.65	179
13	M	41	9.6	2.01		Marked	2	2	1	D 16.7	555	22				7.7	3.50	0.77	185
14	F	40	12.7	3.37		Generalized	0	0	2	D 8.5	333	36	2.10	1		7.2	2.58	1.30	155
15	F	33	9.23	3.76		None	2	0	0	D 10.5	397	22	1.10			5.3		1.50	371
16	F	35				Generalized	0	2	1	Ind 1.1						6.2	2.20	0.55	193
17	M	69	11.3	3.90		Marked	1	1	2	D 3.5	222	20		1		5.7	3.10	1.60	191
18	M	60	17.2	4.22		None	0	0	0	D 2.8	238	16	2.00	1		7.3	3.18	0.53	110
19	M	41	13.1	1.05		Marked	2	3	3	D 25.7		118				5.8	2.88	1.00	191
20	M	36	10.3	3.10		Marked	2	2	1	D 20.0	219	226				1.8	2.01	1.30	190
21	M	47	11.5	3.88		Mild	0	1	3	D 1.6	112	12		3		6.9			185
22	M	54	12.3	4.93		None	0	0	0			66		2		5.5	2.90	1.10	215
23	F	40	11.5	1.17		Marked	1	1	2	D 8.5	333	16		3		7.7	2.00	0.37	260

\* In tables 1 to 3 the basis of grading is 0 to 4, 0 indicates none, and 1 indicates the largest amount  
† D indicates direct reaction, Ind, indirect reaction



## RESULTS

*Subacute and Chronic Atrophy of the Liver with Nodular Regeneration (Cirrhosis)*—A study of 23 patients with cirrhosis of the liver has been made, and the concentration of total protein, the value for albumin and globulin and the colloid osmotic pressure of the serum have been measured in most instances

The clinical data pertaining to these patients are presented in table 1. Chart 1 represents the colloid osmotic pressure of the serum of these 23 patients plotted against the serum protein values. All but 4 of these patients had ascites or edema, most of them had both. In each instance but one the colloid osmotic pressure of the blood serum was below the normal level, but in only 7 instances was the protein value below 6 Gm.

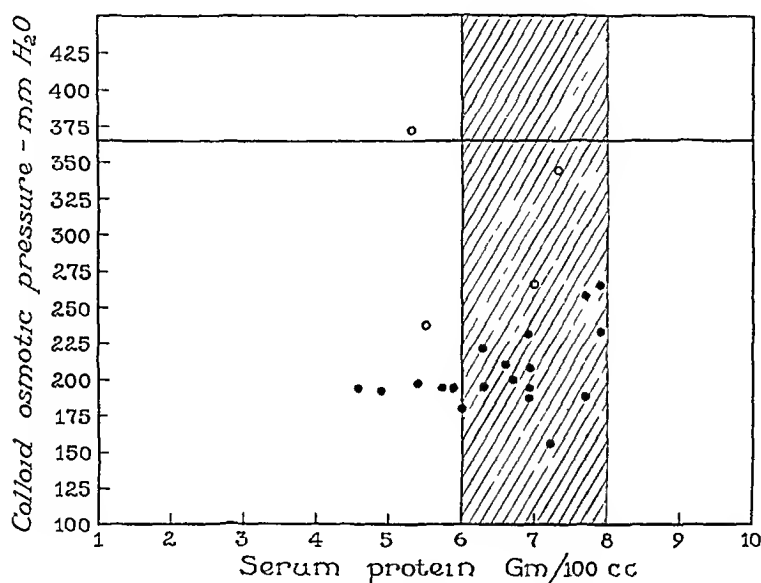


Chart 1—The colloid osmotic pressure of blood serum of patients with hepatic cirrhosis and the relation of this pressure to the concentration of serum protein. In charts 1 and 2 each dot represents the value for 1 patient, the black dots indicating the presence of edema and ascites and the white dots indicating no edema or ascites. The shaded area represents the range of normal concentration of the serum protein. The horizontal line represents the average normal colloid osmotic pressure.

per hundred cubic centimeters. The interesting fact, however, is that 14 of the patients who had edema and ascites and the colloid osmotic pressure of whose serum was low had normal protein values, as determined by standard methods. It is obvious that no exact "edema level" is present and that the determination of the total protein value alone is of little value in predicting the colloid osmotic pressure of the blood serum. In 19 of these 21 cases a better, but still imperfect, correlation between the protein and the colloid osmotic pressure of the serum was obtained by estimation of the albumin content (chart 2). However, in

4 of the cases in which there was ascites or edema (19 per cent of the total represented in chart 2), the albumin content was slightly above or slightly below the lower limit of normal, but the colloid osmotic pressure was 50 per cent or nearly 50 per cent reduced

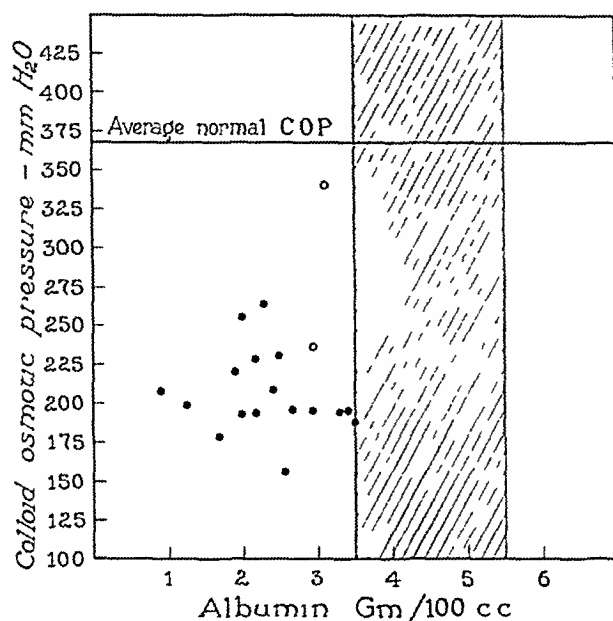


Chart 2—The colloid osmotic pressure of the blood serum of patients with hepatic cirrhosis and the relation of this pressure to the concentration of albumin.

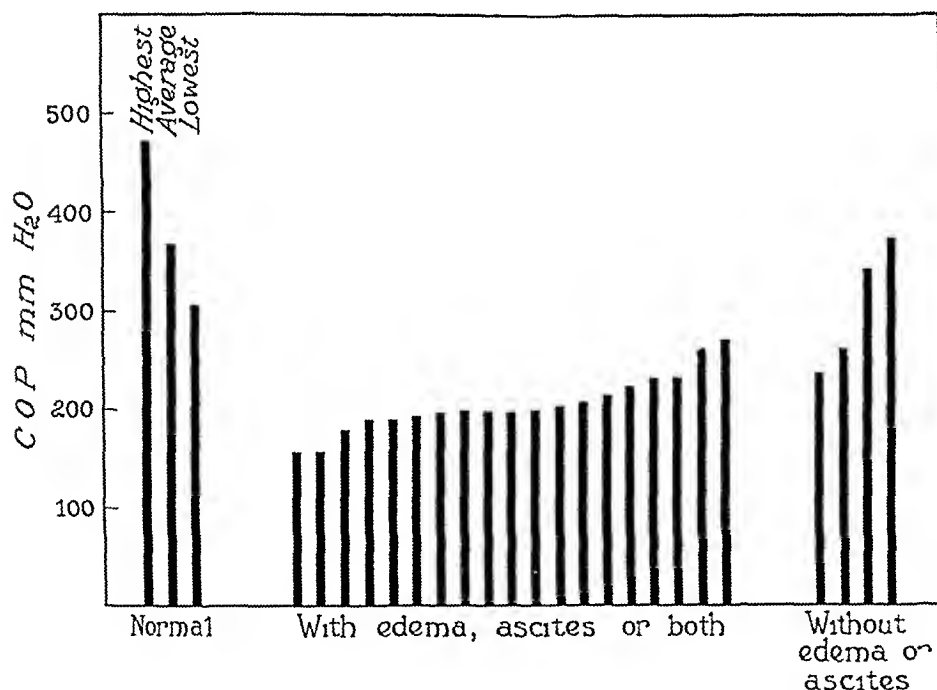


Chart 3—The colloid osmotic pressure of the blood serum of patients with hepatic cirrhosis and the relation of this pressure to the normal values for colloid osmotic pressure. Each column represents the value for 1 patient.

It is interesting to note in chart 3 that the 4 patients who had "compensated" cirrhosis of the liver, without edema or ascites, had in all but 2 instances the highest values for colloid osmotic pressure for the whole group. In none of the cases in which edema and ascites were present did the value for colloid osmotic pressure reach as high as even the lowest level of normal.

Analysis of the laboratory data for these patients (table 1) is of interest. There seems to be some correlation between the value for colloid osmotic pressure and the degree of hepatic damage as estimated by the hepatic functional tests indicated (bromsulphalein, hippuric acid synthesis), and there was evidence of hepatic damage as measured by

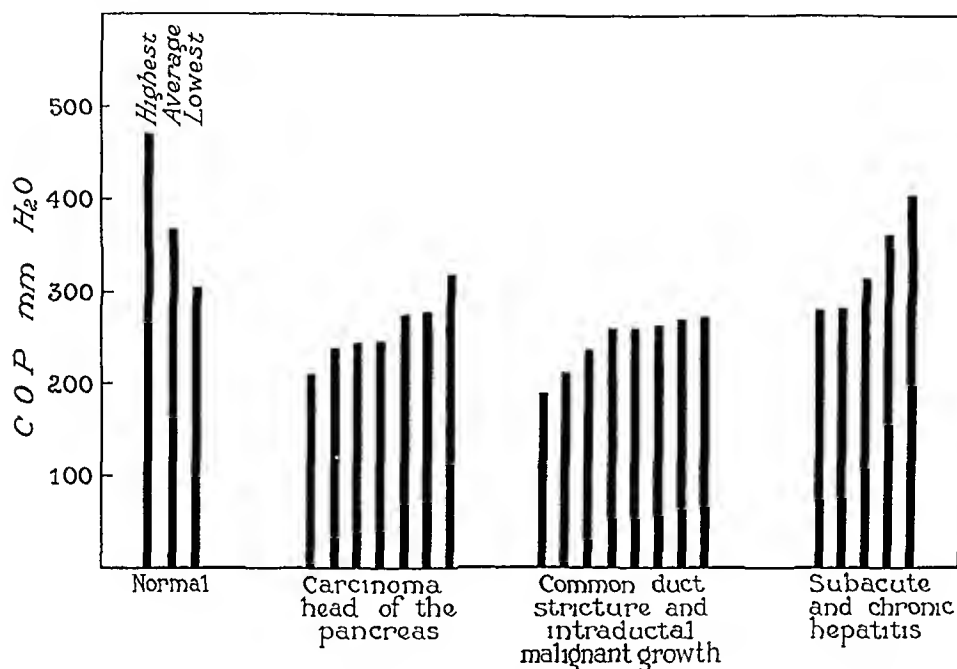


Chart 4—The colloid osmotic pressure of the blood serum of patients with obstructive jaundice and the relation of this pressure to normal values for colloid osmotic pressure

these tests. Obviously, this is not direct evidence that the ability of the liver to make or to store protein is altered, but it does appear that this function of the liver may be impaired somewhat in proportion to the impairment of the ability of the liver to excrete dye or conjugate various materials.

The higher levels for serum bilirubin were associated in most instances with the lower values for colloid osmotic pressure. The alterations in the concentration of cholesterol in the blood did not appear to be connected with the decrease in the serum protein value and the decrease in the colloid osmotic pressure.

TABLE 2—Obstructive Jaundice

Case	Sex	Age, Yr	Hemo- globin, Gm per 100 Cc	Erythro- cytes, Millions per Cu Mm	Macrocytosis	Urine Albu- min, Grade	Edema, Grade	Ascites, Grade	Serum Bilirubin, Mg per 100 Cc	Choles- terol, Mg per 100 Cc	Urea, Mg per 100 Cc	Liver Function			Serum Protein, Gm per 100 Cc	Serum Albumin, Gm per 100 Cc	Albumin Globulin Ratio	Colloid Osmotic Pressure, Mm of Water
												Benzoic Acid, Gm sul- fhydryl Excreted as phalen Hippuric Acid in 4 Hours	Excre- tion, Grade	Excre- tion, Grade				
Carcinoma of Head of Pancreas																		
1	M	67	13.3	3.94		2	0	0	D 22.0			1.60	4		6.5	3.20	1.0	211
2	M	15	10.8	3.43	Slight	2	0	0	D 44.4	7.93	122				6.9	3.71	1.3	271
3	M	46	12.7	3.62	Marked	2	0	0	D 21.0		176				5.4	3.76	2.3	210
4	M	48	12.7	3.59		1	0	0	D 7.9						6.5	3.62	1.3	275
5	F	56	11.2	4.31		1	0	0	D 10.0		20	1.90			7.1	3.49	0.9	318
6	M	31	7.3	2.31	Slight	2	0	0	D 33.0	138	60	2.30			6.0	3.03	1.0	241
7	F	72	7.3	2.54	Not present	2	0	0	D 13.6	181	36				5.7	2.91	1.1	238
Stricture of Common Duct																		
1	F	65	10.8	3.31	Generalized	2	0	0	D 14.5	211	72	1.50			4.9	3.26	1.1	276
2	M	76	12.6	1.07	Generalized	0	0	0	D 6.0	248		4.05			4.73	1.70	1.5	211
3	F	48	11.6	3.07	Slight	1	0	0	D 7.0		18				6.8	2.98	1.8	237
4	F	41	11.9	1.20	Not present	2	1	2	D 5.2		16				7.0	2.70	0.6	273
5	F	63	11.0	3.03	Mild	1	2	2	D 19.3	172	18	1.20			5.7	2.92	1.1	189
6	F	35	12.7	3.10		1	0	0	D 21.7			2.00			6.6	3.07	0.9	260

TABLE 3—Intraductal Malignant Growths and Hepatitis

Case	Sex	Age, Yr	Hemo- globin, Gm per 100 Cc	Erythro- cytes, Millions per Cu Mm	Macrocytosis	Urine Albu- min, Grade	Edema, Grade	Ascites, Grade	Serum Bilirubin, Mg per 100 Cc	Choles- terol, Mg per 100 Cc	Urea, Mg per 100 Cc	Liver Function			Serum Protein, Gm per 100 Cc	Serum Albumin, Gm per 100 Cc	Albumin Globulin Ratio	Colloid Osmotic Pressure, Mm of Water
												Benzole Brom- Acid, Gm sul- fhydryl Excreted as phalen Hippuric Acid in 1 Hours						
												Intraductal Malignant Growth						
1	F	53	12.5	1.14	Slight	0	0	0	D 6.1		34		2	7.10	3.91	1.20	267	
2	M	51	12.3	1.91	Generalized	0	0	0			20		0	5.81	2.91	1.50	235	
Subacute and Chronic Hepatitis																		
1	F	31	10.5	3.33	Slight	1	0	0	D 7.1	362		4.60	3	7.10	2.68	1.00	278	
2	M	62	16.6	4.39	Not present	0	0	0	D 7.5	211	21			6.00	3.37	2.10	282	
3	M	37	10.6	3.57	Marked	0	0	0	D 2.8	116	22	1.10		8.20	2.21	0.37	362	
4	M	15	13.5	1.36	Slight	0	0	0	D 4.3	333	23		1	7.00	3.70	2.50	312	
5	M	25	12.3	4.35	Generalized	1	0	0	D 11.0				0	8.70	4.17	1.30	401	

*Obstructive Jaundice and Subacute and Chronic Hepatitis*—Fifteen patients who had obstructive jaundice and 5 who had various forms of parenchymatous hepatic injury with jaundice were studied. Of the 15 who had obstructive jaundice, 7 had carcinoma of the head of the pancreas, 6 had stricture of the common duct and 2 had an intraductal malignant growth. In each instance the concentration of total protein, the value for albumin and globulin and the colloid osmotic pressure of the serum were measured. The clinical data pertaining to these patients are presented in tables 2 and 3.

TABLE 4—*Ascitic Fluid*

Case	Total Nitrogen, Gm per 100 Cc	Total Protein Nitrogen, Gm per 100 Cc	Albumin Nitrogen, Gm per 100 Cc	Colloid Osmotic Pressure*	Diagnosis
1				153	Cirrhosis of liver
2	1 070			196	Cirrhosis of liver
3				141	Cirrhosis of liver
4				208	Cirrhosis of liver
5				120	Cirrhosis of liver
6	0 725	0 635	0 15		Cirrhosis of liver
7	0 800	0 712	0 23	111	Cirrhosis of liver
8	1 270	1 120	0 33	55	Cirrhosis of liver
9	1 140	1 040	0 32	139	Cirrhosis of liver
10	2 470	2 380	1 18	144	Cirrhosis of liver
11	0 860	0 750	0 51	166	Cirrhosis of liver
12	1 930	1 820	0 375	162	Cirrhosis of liver
13	1 900	1 730	0 63	118	Cirrhosis of liver
14	1 580	1 470	0 76	179	Cirrhosis of liver
15	2 500	2 400	0 51	157	Cirrhosis of liver
16	1 300			118	Nontropical sprue
17	5 800			178	Generalized carcinomatosis
18	4 780			223	Pelvic malignant growth with peritoneal carcinomatosis
19	1 920	1 830	1 40	185	Carcinoma of right kidney, thrombosis of inferior vena cava
20	4 960	4 800	3 23	251	Abdominal carcinoma
21				233	Subacute lymphatic leukemia
22	4 050		3 10	267	Lymphoblastoma, chylous ascites
23	2 830	2 760	1 40	317	Chronic glomerulonephritis
24	1 400	1 280	1 07	106	Hepatitis

\* Millimeters of water per gram of protein nitrogen per hundred cubic centimeters of fluid

In chart 4 it can be observed that the values for colloid osmotic pressure in the cases of obstructive jaundice resulting from carcinoma of the pancreas were higher than they were in the cases of stricture of the common duct and of intraductal malignant growth. It has been our experience that for some reason greater hepatic injury results from simple stricture of the common duct than from carcinoma of the head of the pancreas. In the cases of the latter type the early damage results in disturbed protein metabolism and probably accounts for the "water-logging" not infrequently encountered during treatment. In the cases of "hepatitis" the colloid osmotic pressure is higher than in either of the two types of cases included under the heading obstructive jaundice, probably because in such cases as subacute and chronic hepatitis the

damage to the liver is minimal and of a chronic nature. The values for cholesterol for the patients who had hepatitis were all above normal.

*The Formation, the Protein Content and the Colloid Osmotic Pressure of Ascitic Fluid*—It is fairly well established that the concentrations of urea, uric acid, creatinine, chloride and sugar of the ascitic fluid approximate closely the concentrations of these substances in the blood serum, the cholesterol content varies greatly.<sup>27</sup> The protein content of pure transudates usually is low, but if it is high one can safely consider that some exudative process is present. As far as we are aware, the cases represented in table 4 are the only instances in which the colloid osmotic pressure of ascitic fluid has been measured. It is interesting that even with such low concentrations of protein and albumin these transudates exert a comparatively high colloid osmotic pressure. The probable explanation of this is that the smaller molecules of albumin are the first to escape through the capillary wall, and these of course exert the greatest osmotic effect. In the group as a whole it may be observed that most of the higher values for colloid osmotic pressure are those in which at least part of the ascitic fluid is formed by an exudative process.

#### COMMENT

As was pointed out in an earlier paragraph, there is considerable experimental and clinical evidence to indicate that the protein of blood may be altered quantitatively and qualitatively by the presence of hepatic disease, and if this fact may be assumed, the diminution of colloid osmotic pressure is not difficult to explain. The existence of hypoalbuminemia would in itself explain the low colloid osmotic pressure, since the smaller molecules of protein are the ones which exert the greater osmotic effect. The exact mechanism which brings about this deficiency is unknown, but presumably in these cases it is closely related to hepatic injury. Although the alteration in the colloid osmotic pressure of the blood serum is not the sole factor in production of edema and ascites in some of these diseases, it is certainly important and must be evaluated in order to permit an understanding of the existing abnormalities in distribution of fluid between blood and tissues.

Enough is known of the relation of plasma protein to the distribution of the body fluids to assume that the low levels encountered in hepatic disease are not without some effect on the production of ascites and edema. The formation of excessive ascitic fluid usually involves a disturbance of one or several factors. There can be a decrease in the

<sup>27</sup> Foord, A. G., Youngberg, G. E., and Wetmore, V. The Chemistry and Cytology of Serous Fluids, *J. Lab. & Clin. Med.* **14**: 417, 1929.

colloid osmotic pressure, increased venous pressure, impaired drainage of lymph or increased capillary permeability. In hepatic disease there are present frequently a low colloid osmotic pressure and perhaps an increased portal venous pressure and increased capillary permeability.

There is good anatomic evidence to indicate that in cirrhosis of the liver there is an increased venous pressure in the portal system, but few direct measurements are on record. McIndoe,<sup>28</sup> working on livers obtained at necropsy from patients with portal cirrhosis, observed that when the livers were perfused through the portal vein with physiologic solution of sodium chloride at a pressure of 260 to 400 mm of water, only about a third of the solution flowed out of the hepatic vein. Thompson and others<sup>29</sup> measured the pressure in the splenic vein by direct readings at operation on patients with Banti's syndrome associated with cirrhosis of the liver. The average pressure in the splenic vein was 360 mm of water, in contrast to the 117 mm of water observed for the controls. In our series of cases of cirrhosis of the liver the colloid osmotic pressure averaged between 200 and 250 mm of water, values below the average for portal venous pressure determined experimentally. It is probable, then, that in cirrhosis of the liver the pressure in the portal system exceeds the colloid osmotic pressure in the blood, thus producing an abnormally high hydrostatic pressure in the capillaries, while the effective osmotic pressure of the blood is either normal or secondarily diminished. The osmotic equilibrium thus is disturbed in a manner favoring transudation. There are other cases, however, in which reduction of the colloid osmotic pressure is a primary factor. In cirrhosis of the liver the tendency toward formation of excessive ascitic fluid possibly can be explained by the increased venous pressure in the portal system in addition to the reduction in the colloid osmotic pressure and the possible injury of the capillary membrane. However, there are some experimental results which indicate that the process is not so simple. In some recent unpublished studies on experimentally produced cirrhosis in dogs, Bollman<sup>30</sup> found that the appearance of ascites and edema was not directly related to any exact protein value ("edema level") or level of colloid osmotic pressure. The rapidity of transudation of fluid was more directly related to the extent of the hepatic injury.

#### SUMMARY

The molecular activity of the serum protein as measured by the colloid osmotic pressure was studied in examining patients with cirrhosis

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28 McIndoe, A. H. Vascular Lesions of Portal Cirrhosis, *Arch. Path.* **5**: 23, 1928.

29 Thompson, W. P., Caughey, J. L., Whipple, A. O., and Rousselot, L. M. Splenic Vein Pressure in Congestive Splenomegaly (Banti's Syndrome), *J. Clin. Investigation* **16**: 571, 1937.

30 Bollman, J. L. Personal communication to the authors.

of the liver on various forms of obstructive jaundice. Similar studies were applied to ascitic fluid from various sources.

The colloid osmotic pressure of the serum of patients with chronic atrophy of the liver (cirrhosis) often was reduced to half the normal value. In some cases in which edema and ascites were present the value for colloid osmotic pressure was lower than the estimated hydrostatic pressure of the portal venous system. For patients with obstructive jaundice the values for colloid osmotic pressure also were substantially reduced, often without respect to the depth of jaundice in the individual case.

In all the types of conditions studied there was no constant relation between the level of serum protein and the colloid osmotic pressure, there was, as might have been predicted, better correlation between osmotic pressure and concentration of serum albumin. In hepatic disease no constant "edema level," as measured by the colloid osmotic pressure, could be demonstrated.



# EFFECT OF LARGE DOSES OF INSULIN ON THE PROTEINS AND THE COLLOID OSMOTIC PRESSURE OF BLOOD SERUM

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AND

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The recent widespread use of "insulin shock" therapy for schizophrenia (dementia praecox) makes it desirable to evaluate more precisely the effects of large doses of insulin on the protein in the blood serum of human beings. Traumatic and the other more common types of shock are characterized by general hemoconcentration involving both red blood cells and plasma protein, the clinical sequence of falling blood pressure, rising pulse rate and circulatory collapse is referable to a loss of fluid from the blood to the tissues. It is not at all certain that any similar loss of fluid occurs in "insulin shock."

The term insulin anhydremia has been used to describe the effect of insulin in bringing about a rapid and large increase in the hemoglobin concentration of the blood<sup>1</sup>. It is doubtful whether this designation is applicable, because, in contrast with the changes in the hemoglobin concentration, variable changes in the plasma protein content have been reported.

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This work was done in the Division of Biochemistry of the Mayo Foundation, and this paper represents part of the work for which the John Horsley Memorial Prize for 1938 was awarded to Dr. Butt by the University of Virginia.

1 (a) Drabkin, D. L., and Edwards, D. J. The Production of Anhydremia with Insulin, *Am J Physiol* **70** 273, 1924. (b) Klein, O. Zur hormonalen Beeinflussung des Wasserhaushaltes beim Diabetes mellitus durch Insulin und Pituitrin, *Ztschr f klin Med* **100** 458, 1924. (c) Staub, H. Insulin zur Einfuhrung in die Insulintherapie des Diabetes mellitus, Berlin, Julius Springer, 1924, p. 63. (d) Yamaguchi, T. Studien uber Flussigkeitsaustausch. V. Hormonale Beeinflussung des intermediaren Flussigkeitsaustausches im gesunden und sogenannten merenkranken Zustande des Hundes, *Tohoku J Exper Med* **9** 551, 1927. (e) Drabkin, D. L., and Shilkret, H. Insulin Anhydremia. Importance of the Water-Reserve in Physiological Crisis, *Am J Physiol* **83** 141, 1927. (f) Kimura, K., and Takahashi, H. Beeinflussung des Stoffumsatzes quergestreifter Muskeln durch direkte Einwirkung von Insulin. Ein Beitrag zur Frage des Wirkungsmechanismus von Insulin, *Tohoku J Exper Med* **10** 215, 1928. (g) Winter, F. Ueber den Einfluss des Insulins auf den Wasserstoffwechsel des Gesunden und Diabetikers, *Acta med Scandinav* **80** 136, 1933.

Klein and Kment<sup>2</sup> administered from 40 to 80 units of insulin to patients with disease of the liver and obtained variable responses in the plasma protein content. Taubenhaus and Rosenzweig<sup>3</sup> reported that the concentration of plasma protein increased slightly in most of their 16 patients who received from 20 to 40 units of insulin. The latter authors agreed with Klein and Kment<sup>2</sup> that the globulin fraction tends to increase. In a preliminary paper on "insulin shock" therapy Zozaya<sup>4</sup> stated, without giving details: "We notice a marked increase in the total protein at the coma."

Inconsistent results have been reported from animal experiments. Sakurai, Horiyama and Inoue<sup>5</sup> found that insulin usually produces a slight decrease in the plasma protein value for rabbits. Kerr<sup>6</sup> reported a decrease of about 1 per cent in dogs after injection of 10 to 80 units of insulin, but Kikuta,<sup>7</sup> also working with dogs, reported a slight increase in the concentration of protein in the plasma.

There is even less agreement about the effect of insulin on the colloid osmotic pressure of the blood serum. After the injection of insulin into rabbits Kylin<sup>8</sup> found an initial decrease of 8 to 43 mm of water, followed by a secondary rise. Tada and Nakazawa<sup>9</sup> reported exactly the opposite result, while Oelkers<sup>10</sup> could find no effect at all.

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2 Klein, O., and Kment, M. Beobachtungen über Insulin-Hypoglykämie beim Menschen. III. Verhalten der Eiweissfraktionen des Blutes, des Bilirubins, der Blutkonzentration und der Blutgerinnung, insbesondere bei Leberkranken, *Ztschr f klin Med* **107**:476, 1928.

3 Taubenhaus, M., and Rosenzweig, S. Ueber die Wirkung des Insulins auf das Bluteiweissbild und deren Beeinflussung durch Kohlehydratgaben und Coffein, *Ztschr f klin Med* **118** 719, 1931.

4 Zozaya, J. Physicochemical Changes in Blood Serum of Patients with Schizophrenia Treated by Hypoglycemic Shock, *Proc Soc Exper Biol & Med* **37** 327, 1937.

5 Sakurai, T., Horiyama, A., and Inoue, K. Ueber den Einfluss des Insulins auf einige Bestandteile des Blutserums, *J Biochem* **4** 333, 1924.

6 Kerr, S. E. The Effect of Insulin and of Pancreatectomy on the Distribution of Phosphorus and Potassium in the Blood, *J Biol Chem* **78** 35, 1928.

7 Kikuta, T. Vergleichende Untersuchungen über die Veränderungen des Zucker-, Milchsäure- und Eiweissspiegels in der Lymphe sowie im Blut, ein Beitrag zur Kenntnis des intermediären Kohlehydratstoffwechsels in der Leber. I. Insulinwirkung, *Tohoku J Exper Med* **25** 148, 1935.

8 Kylin, E. Studien über den kolloidosmotischen (onkotischen) Druck. XVII. Ueber den Einfluss des Insulins auf den kolloidosmotischen Druck, *Arch f exper Path u Pharmacol* **161** 692, 1931.

9 Tada, S., and Nakazawa, F. Hormonale Beeinflussung des kolloidosmotischen Drucks des Bluts, *Tohoku J Exper Med* **15** 119, 1930.

10 Oelkers, H. A. Hormonale Beeinflussung des kolloid-osmotischen Drucks, kolloid-osmotischer Druck und Diurese, *Arch f exper Path u Pharmacol* **160** 9, 1931.

A study of the insulin therapy for schizophrenia at the Mayo Clinic (Rosenberg and others<sup>11</sup>) afforded an opportunity to study these questions on physically normal subjects receiving large doses of insulin

#### METHODS

The subjects were physically normal men with schizophrenia. They were all in relatively robust general health and had been selected as suitable for study after several months of institutional life, including the taking of a standard institutional diet. Studies were also carried out on dogs which were accustomed to the procedures of bleeding and injection.

All the studies on men were made while the subject was at rest in bed and fasting. Blood was drawn into an oiled syringe from the antecubital vein immediately before the hypodermic injection of from 20 to 130 units of insulin. With one or two exceptions, marked signs of "insulin shock" developed. A second sample of blood was drawn at the height of the insulin reaction, from one to two hours later.

The blood sugar value was determined for fresh whole blood by means of the Shaffer-Somogyi<sup>12</sup> modification of the Shaffer-Hartmann<sup>13</sup> method. The rest of the blood was allowed to clot, and the serum was separated immediately thereafter. The protein content of the serum was estimated by the standard Kjeldahl procedure, and the method of Howe<sup>14</sup> was used for the separation of albumin and globulin.

The colloid osmotic pressure of the blood serum was measured by a modification of the membrane bag arrangement used by Starling,<sup>15</sup> Adair<sup>16</sup> and others. The details of the method will be presented elsewhere, but a few essentials may be given here. The serum was diluted with an equal volume of a phosphate buffer solution at  $pH$  7.4, which was approximately isoionic and iso-osmotic with the serum. Small, fairly rigid collodion sacs were used which had been previously tested and shown to be protein tight. The same buffer solution was used for the external medium, and the entire system was kept at 0 C. Usually equilibration was complete within forty-eight hours, but in all cases the osmometers were observed several days longer. At the end of equilibration the nitrogen content was determined in both inner and outer fluids and compared with the protein and nonprotein nitrogen values for the original serum. Values for the total colloid

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11 Rosenberg, E. F., Smith, B. F., Wilder, R. M., and Moersch, F. P. Treatment of Schizophrenia (Dementia Praecox) by Insulin Hypoglycemia. I. Preliminary Report, Proc. Staff Meet., Mayo Clin. **12**: 273, 1937.

12 Shaffer, P. A., and Somogyi, M. Copper-Iodometric Reagents for Sugar Determination, J. Biol. Chem. **100**: 695, 1933.

13 Shaffer, P. A., and Hartmann, A. F. The Iodometric Determination of Copper and Its Use in Sugar Analysis. II. Methods for the Determination of Reducing Sugars in Blood, Urine, Milk, and Other Solutions, J. Biol. Chem. **45**: 365, 1921.

14 Howe, P. E. The Determination of Proteins in Blood—A Micro Method, J. Biol. Chem. **49**: 109, 1921.

15 Starling, E. H. On the Absorption of Fluids from the Connective Tissue Spaces, J. Physiol. **19**: 312, 1896.

16 Adair, G. S. Direct Method of Measuring the Osmotic Pressure of Hemoglobin, Proc. Roy. Soc., London **108**: 627, 1925.

osmotic pressure were corrected to the original concentration of protein in the serum by means of standard curves for protein dilution (Keys<sup>17</sup> and Keys and Butt<sup>18</sup>) All determinations were made in duplicate

## RESULTS

The results of the studies on the schizophrenic men are summarized in table 1 In every case both the concentration of total protein

TABLE 1—*Changes in Protein Concentration and Colloid Osmotic Pressure of the Blood Serum of Man After the Intramuscular Injection of Large Doses of Insulin*

Subject	Sample and Time*	Units of Insulin	Blood Redueing Substance as Sugar, Mg per 100 Ce	Blood Serum					
				Total Protein, Gm per 100 Ce	Change in Total Protein, %	Albumin Nitrogen, Mg per 100 Ce	Change in Albumin Nitrogen, %	Total Colloid Osmotie Pressure, Mm of Water	Change in Colloid Osmotie Pressure, %
M	R	90	102	6.20		620		264	
	72		22	6.39	+ 3.1	635	+ 2.1	285	+ 8.0
M <sub>1</sub>	R	60	108	6.32		618		244	
	98		39	6.48	+ 2.5	649	+ 5.0	252	+ 4.9
L	R	60		7.04		680			
	67		33	7.41	+ 5.3	740	+ 8.8	373	
ME	R	20	110	6.73		697		288	
	85		83	6.79	+ 0.9	758	+ 8.8		
G	R	70		6.80		646		284	
	75		22	6.88	+ 1.2	718	+11.1	319	+12.3
G <sub>1</sub>	R	60	100	6.73		612		289	
	97		39	6.84	+ 1.6	643	+ 5.1	321	+11.1
P	R	130	107	6.85		631		320	
	102		62	7.17	+ 4.7	664	+ 5.2	350	+ 9.4
P <sub>1</sub>	R	120	110	6.57		699		283	
	125		50	7.25	+10.3	706	+ 1.0	300	+ 5.7
H	R	70	114	7.03		650	-13.5	305	
	71		31	7.51	+ 6.8	738		320	+ 4.9
	94			7.04	+ 0.2	656	+ 5.5		
H <sub>1</sub>	R	70	111	7.02		700		305	
	60		40	7.67	+ 9.3	718	+ 2.6	328	+ 7.5
H <sub>2</sub>	R	60	98	6.02		618		264	
	45		48	6.77	+12.6	600	- 2.9	324	+22.8
Mean changes					+ 5.3		+ 5.5		+ 9.7

\* R indicates the sample taken immediately preceding the injection of insulin The numbers indicate the number of minutes after the injection of insulin

in the serum and the colloid osmotic pressure rose The rise in colloid osmotic pressure was beyond the experimental error for all the patients, with the possible exception of M<sub>1</sub>, while the rise in the serum protein value could be considered doubtful in the studies on ME, G and possibly G<sub>1</sub> In another series of studies of 9 patients we found an average rise of 4.2 per cent in the concentration of serum protein with a range from +0.3 to +10.4 per cent

17 Keys, A The Study of Colloidal Dimensions, Thermodynamic Activity, and the Mean Molecular Weight of the Mixed Proteins in Blood Serum, J Phys Chem 42 11, 1938

18 Keys, A and Butt H R Unpublished data

There can be no doubt that in subjects with this type of condition at least, the injection of 20 to 130 units of insulin results in a small but significant rise in the concentration of total plasma protein. This increase was considerably less than would correspond with some of the changes in hemoglobin concentration, which ranged up to from 20 to 40 per cent, if both processes were the result of a simple loss of water from the blood.

It will be noted that the albumin value appeared to change on the average in proportion to the total protein content, but there were considerable deviations in individual experiments. Both practical experience and theory, however, lead one to view quantitative estimations of

TABLE 2—*Changes in Protein Concentration and Colloid Osmotic Pressure in Dogs After the Intramuscular Injection of One Unit of Insulin per Kilogram of Body Weight*

Dog	Sample*	Blood Reducing Substance as Sugar, Mg per 100 Cc	Total Serum Protein, Gm per 100 Cc	Change in Total Protein, %	Albumin Nitrogen, Mg per 100 Cc	Change in Albumin Nitrogen, %	Colloid Osmotic Pressure, Mm of Water	Change in Colloid Osmotic Pressure, %
A	Before	62	5.75		448			
	After	26	7.08	+23.1	512	+14.3	283	
B†	Before	64	6.17		523		235	
	After	35	6.23	+1.0	492	-5.9	249	+6.0
C†	Before	70	6.99		595		299	
	After	33	6.68	-4.4	460	-22.7	261	-12.7
D	Before	80	6.22				228	
	After	30	6.04	-2.9			225	-1.3
O	Before	98	5.96		628		263	
	After	49	6.71	+12.6	607	-3.3	323	+22.8
Mean changes				+5.9		-4.4		+3.7

\* In each case the first sample was taken immediately before the insulin was injected and the second sample forty-five minutes later.

† In these cases the stellate ganglions had been removed long before the present experiments were performed.

“albumin” with much suspicion. The fraction of the protein which precipitates when a given amount of a foreign salt is added is only too easily influenced by alterations in the other electrolytes, the  $p_H$ , the temperature and the time factors to justify any reliance on this method of so-called fractionation of proteins. It can be said, however, that the changes in the “albumin” are of the same order as the changes in the total protein content.

For comparison with the studies on man we carried out experiments on 5 dogs, the results are summarized in table 2. The results were much more variable than those obtained for human beings, we are unable to explain this difference other than by stating that in our experience results from animal experimentation are almost always more variable than the results of studies on human beings. It should be pointed out that though both the men and the dogs were accustomed

to injections and venipuncture, the men were unquestionably less excited by the procedures

The blood sugar values given in tables 1 and 2 are actually only values for reducing substance. By the method used, nondextrose reducing substances (such as glutathione and ascorbic acid) account for something like 20 to 30 mg of the reported "blood sugar" value. This means that, except for the studies on subject P, the value for sugar in the blood after the administration of insulin declined practically to the vanishing point.

It is of interest to note that subject P, who received the largest doses of insulin, was extremely resistant to the hormone so far as could be judged from his general response and the effect on the level of sugar in the blood. In spite of this fact the changes in the serum protein value and the colloid osmotic pressure were similar to the changes seen in the other subjects.

#### THE SIGNIFICANCE OF ALTERATIONS IN THE COLLOID OSMOTIC PRESSURE

Alterations in the volume of blood as a result of injection of insulin have been argued, chiefly on the basis of changes in the concentration of hemoglobin. Drabkin and Edwards<sup>19</sup> and Levine and Kolars<sup>10</sup> claimed that insulin produces anhydremia in both dogs and rabbits, Haldane and others<sup>20</sup> and Olmsted and Taylor<sup>21</sup> reported an opposite effect, while Hamilton and his colleagues<sup>22</sup> found no change. These differences in results may be due to the different experimental conditions, animals and methods involved. The changes in the protein concentration of the serum reported here might be taken to indicate a slight but consistent reduction in blood volume. However, the changes in colloid osmotic pressure must be taken into account.

Since the colloid osmotic pressure rose, in per cent terms, appreciably more than did the concentration of serum protein, it might be thought that the blood had been enriched with a new supply of protein of low molecular weight. This simple argument, however, neglects

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19 Levine, V. E., and Kolars, J. J. The Effect of Insulin on the Morphological Blood Picture, with a Note on the Relation of Diet to the Convulsions Induced by Insulin, *Am J Physiol* **74** 695, 1925.

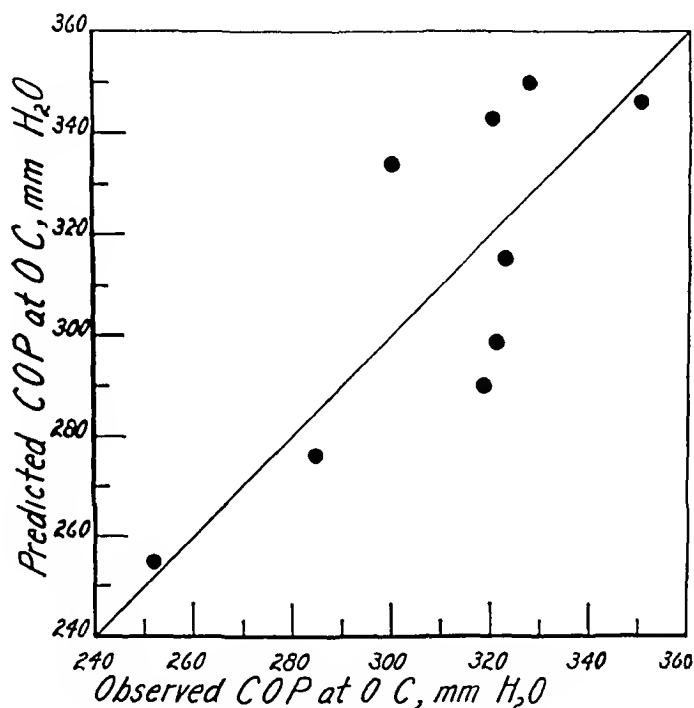
20 Haldane, J. B. S., Kay, H. D., and Smith, W. The Effect of Insulin on Blood Volume, *J Physiol* **59** 193, 1924.

21 Olmsted, J. M. D., and Taylor, A. C. The Effect of Insulin on the Blood. I. Changes in Oxygen Saturation, Percentage Hemoglobin and Oxygen Capacity, *Am J Physiol* **69** 142, 1924.

22 Hamilton, W. F., Barbour, H. G., and Warner, J. H. Does Insulin Significantly Affect the Blood Concentration? *J Pharmacol & Exper Therap* **24** 335, 1924.

the fact that the osmotic activity per unit of protein of the mixed serum proteins increases with increasing concentration. This effect may be allowed for approximately in calculation by the use of the tables developed by Keys<sup>17</sup>

The accompanying chart shows the relation between the observed colloid osmotic pressure after the administration of insulin and the colloid osmotic pressure which would be predicted from the protein concentration on the assumption that no change in the state of aggregation occurs. In other words, the values plotted on the ordinate in chart 1 are the values which would have been obtained if the protein



Comparison of observed colloid osmotic pressure of the blood serum of men after the injection of insulin with the colloid osmotic pressure predicted from the change in concentration of total protein in the serum, assuming no alteration in the mean molecular weight

concentration in the serum had been changed simply by an alteration of the amount of water in the system. The method of calculation is simple.  $\text{Predicted COP}_2 = \text{COP}_1 \times \frac{C_2}{C_1} \times \frac{f_2}{f_1}$ , the subscripts 1 and 2 referring to values before and after the administration of insulin, C referring to the concentration of total protein in the serum and the values for f, corresponding to the values for C, being taken from table 2 in a previously published paper<sup>17</sup>

In spite of the fact that a number of the individual predictions differ significantly from the observed colloid osmotic pressure in "insulin shock," there is no consistent trend of difference. The mean predicted

value for the colloid osmotic pressure, assuming no change in the serum protein content, in the complete studies of 9 men was 312 mm of water, as compared with an observed mean value of 311 mm. The observed mean value before the administration of insulin in the same studies was 284 mm of water (at 0 C). It is clear that on the average there was no change in the physical state of aggregation of the proteins and that the mean molecular weight of the mixed proteins in the serum was not altered.

These findings place definite limitations on the possible alterations in blood volume in these studies. In view of the large increases in concentration of hemoglobin frequently observed in "insulin shock," a possible decrease in blood volume may be considered. A decrease in blood volume may be brought about (1) by a loss of pure whole plasma to the tissues, (2) by a loss of protein-free fluid to the tissues and (3) by a loss of fluid containing some of the smaller and therefore more filterable proteins to the tissues. A loss of pure whole plasma may be ruled out, as this occurs only in rare terminal conditions when the integrity of the capillary membrane is completely destroyed. The analysis of the measurements of the colloid osmotic pressure rules out the third possibility (differential filtration). Accordingly the only way in which a decrease of blood volume could have occurred must have been by the loss of protein-free fluid from the blood to the tissues.

The general order of magnitude of this loss of protein-free fluid may be calculated if it is assumed that no additional protein entered the blood stream during the experimental period. Two reasons may be adduced in support of this assumption. 1. There are no known reservoirs of protein which can contribute, in the space of an hour or so, appreciable supplies of new protein to plasma which already has a normal protein level. 2. If new protein were added it would be surprising if it had precisely the same mean molecular weight as the protein already in the blood stream. On this assumption there was an indicated average reduction of about 5 per cent in the plasma volume, of about 130 cc of fluid in a man weighing about 60 Kg. This would account for an increase in the hemoglobin concentration of only about 3 per cent. There seems to be no alternative to the conclusion that the principal change in the concentration of blood is referable to an addition of red blood cells from reservoirs such as the spleen and liver and a small loss of fluid from the plasma. It seems improbable that any significant change in the total blood volume occurs.

#### COMMENT

"Insulin shock" has come to be the most common term used to designate the clinical manifestations of extreme hypoglycemia follow-



ing administration of insulin. In other conditions of shock—surgical, burn and cholera shock—the most characteristic and significant feature is a marked loss of fluid from the vascular system. In this respect “insulin shock” is different. It is notable that in “insulin shock” the pulse rate shows only a slight to moderate increase and the blood pressure, though more variable than normal and frequently somewhat low, never falls to the level associated with other types of shock (Stokvis<sup>23</sup>). It seems preferable to refer to this condition as insulin collapse or to use some other term which does not imply a relation to the more common types of shock.

Another point of differentiation between insulin collapse and the shock state is in the oxygen saturation of the blood. In severe traumatic shock, for example, the venous blood frequently has a low saturation. We have found, however, that the oxygen saturation of venous blood from the arm in insulin collapse is high and even approaches the arterial level. In 2 cases the values before insulin was given were 62 and 76 per cent, respectively, during the height of the reaction the values were 79 and 84 per cent, respectively.

#### SUMMARY

The effect of injections of insulin on the protein content and the colloid osmotic pressure of the blood serum was studied in physically normal men with schizophrenia and in dogs. Doses of 1 unit of insulin per kilogram of body weight were used for the dogs and doses of 20 to 130 units for the men.

In all cases after the administration of insulin there was a rise in the concentration of total serum protein, in nineteen studies on men this increase averaged 47 per cent. On the average the albumin concentration changed in proportion to the total protein content.

In all cases there was an increase in the colloid osmotic pressure of the serum of the men, the average rise for nine studies was 97 per cent. Calculations are presented to show that on the average the mean molecular weight of the serum protein is unchanged in acute insulin hypoglycemia.

It is concluded that “insulin shock” bears no close relation to other types of shock, that the total blood volume is at most only slightly altered and that the principal change in the blood concentration is a result of the addition of new red blood cells to the active circulation.

Dr. B. F. Smith made it possible for us to use the facilities of the Rochester State Hospital. Dr. E. F. Rosenberg cooperated in the study of the schizophrenic subjects, and Dr. W. C. Corwin, fellow in the Mayo Foundation, carried out the procedures on the dogs.

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<sup>23</sup> Stokvis, B. Registration of Blood Pressure During Insulin Shock in Schizophrenic Patients, *Nederl tijdschr v geneesk* 81 4373, 1937.

# FILTRATION PROCESSES IN EXTREMITIES DUE TO STANDING, OSMOTIC ACTIVITY OF PLASMA LIPOIDS

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Quiet standing results in hemoconcentration, generally referred to a loss of fluid by transudation to the tissue spaces of the extremities<sup>1</sup> The alterations in the blood are similar to those produced by simple venous stasis<sup>2</sup> Along with a general rise in the concentration of the

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This work was done in the Division of Biochemistry of the Mayo Foundation, and this paper represents part of the work for which the John Horsley Memorial Prize for 1938 was awarded to Dr Butt by the University of Virginia

1 (a) Carrier, E B, and Rehberg, P B Capillary and Venous Pressure in Man, *Skandinav Arch f Physiol* **44** 20, 1923 (b) Thompson, W O, Thompson, P K, and Dailey, M E The Effect of Posture on the Composition and Volume of the Blood in Man, *J Clin Investigation* **5** 573, 1928, (c) The Effect of Posture upon the Composition and Volume of the Blood in Man, *Proc Nat Acad Sc* **14** 94, 1928 (d) Drury, A N, and Jones, N W Observations upon the Rate at Which Oedema Forms When the Veins of the Human Limb Are Congested, *Heart* **14** 55, 1927 (e) Harrop, G A, Jr, and Waterfield, R L The Effect of Posture on the Composition and Volume of the Blood and on Its Selective Diffusion into the Lymph Spaces, *J Physiol* **70** xxxii, 1930 (f) Turner, A H, Newton, M I, and Haynes, F W The Circulatory Reaction to Gravity in Healthy Young Women Evidence Regarding Its Precision and Its Instability, *Am J Physiol* **94** 507, 1930 (g) Waterfield, R L The Effects of Posture on the Circulating Blood Volume, *J Physiol* **72** 110, 1931

2 (a) Bohme, A Ueber die Schwankungen der Serumkonzentration beim gesunden Menschen, *Deutsches Arch f klin Med* **103** 522, 1911 (b) Rowe, A H The Effect of Venous Stasis on the Proteins of Human Blood Serum, *J Lab & Clin Med* **1** 485, 1916 (c) Mende, D Ueber Hyperamie und Oedem bei der Hemmung der Ruckflusses des venosen Blutes durch die Staubinde, *Deutsche Ztschr f Chir* **150** 379, 1919 (d) Krogh, A, Landis, E M, and Turner, A H The Movement of Fluid Through the Human Capillary Wall in Relation to Venous Pressure and to the Colloid Osmotic Pressure of the Blood, *J Clin Investigation* **11** 63, 1932 (e) Landis, E M, Jonas, L, Angevine, M, and Erb, W The Passage of Fluid and Protein Through the Human Capillary Wall During Venous Congestion, *ibid* **11** 717, 1932 (f) Landis, E M, and Gibbon, J H, Jr The Effects of Temperature and of Tissue Pressure on the Movement of Fluid Through the Human Capillary Wall, *ibid* **12** 105, 1933

blood there is a marked increase in the colloid osmotic pressure of the serum under these conditions <sup>3</sup>

Man and Peters <sup>4</sup> found that the rise in the concentration of plasma protein with standing is paralleled, in general, by rises in the concentrations of cholesterol, fatty acids and lipid phosphorus in the serum. They concluded that the capillaries are equally impermeable to all these substances. This conclusion is important enough to warrant independent confirmation. In particular it appears that possible osmotic consequences should be studied.

There is still some uncertainty as to whether the capillaries are, under these conditions, completely impermeable to protein. Thompson, Thompson and Dailey <sup>1c</sup> compared measurements of the plasma volume by the dye method with concentrations of serum protein and concluded that the transudate is free from protein. This was denied by Waterfield <sup>1s</sup> on the basis of measurements of blood volume by the carbon monoxide method. Krogh, Landis and Turner <sup>2d</sup> found that significant leakage of protein occurs in venous stasis when the pressure exceeds 70 cm of water. During quiet standing the venous pressure in the foot is ordinarily of the order of 90 to 120 cm of water (Youmans and others <sup>3b</sup>). Youmans and his colleagues did not find alterations in the albumin-globulin ratio in the serum after standing, but measurements of albumin and globulin supply scarcely satisfactory evidence to warrant the conclusion that no differential filtration occurred. Results of studies on albumin and globulin in venous stasis are not entirely consistent <sup>5</sup>.

#### EXPERIMENTAL PROCEDURE

For our studies normal young men and a normal young woman served as subjects. All the studies were carried out in the morning with the subject in the postabsorptive state. After thirty minutes of rest in bed a sample of blood was taken from the arm, the bed was tipped, and samples of blood were taken from the arm and foot after twelve to thirty-five minutes. In the first experiments angles of 65 to 85 degrees from the horizontal were used, but in the main

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3 (a) Ni, T. G., and Rehberg, P. B. On the Influence of Posture on Kidney Function, *J. Physiol.* **71** 331, 1931. (b) Youmans, J. B., Wells, H. S., Donley, D., and Miller, D. G. The Effect of Posture (Standing) on the Serum Protein Concentration and Colloid Osmotic Pressure of Blood from the Foot in Relation to the Formation of Edema, *J. Clin. Investigation* **13** 447, 1934. (c) Wells, H. S., Youmans, J. B., and Miller, D. G. A Formula and Nomogram for the Estimation of the Osmotic Pressure of Colloids from the Albumin and Total Protein Concentrations of Human Blood Sera, *ibid.* **12** 1103, 1933. (d) Krogh, Landis and Turner <sup>2d</sup>.

4 Man, E. B., and Peters, J. P. Permeability of 'Capillaries' to Plasma Lipids, *J. Clin. Investigation* **12** 1031, 1933.

5 Plass, E. D., and Rourke, M. D. The Effect of Venous Stasis on the Proteins of Blood Plasma and on the Rate of Sedimentation of the Red Blood Corpuscles, *J. Lab. & Clin. Med.* **12** 735, 1927. Rowe <sup>2b</sup>.

series of studies an angle of 54 degrees was used. The less acute angle was preferred because the subject remained comfortable and well relaxed and the changes in concentration were no different from those seen with the more acute angle of posture.

All samples of blood were taken without any externally applied stasis. The blood was drawn into an oiled syringe and immediately transferred to centrifuge tubes with heparin for measurements of whole blood and without heparin for separation of serum.

#### METHODS

The hemoglobin value was estimated by means of the oxygen capacity and in some cases by the photometric method of Sanford and Sheard. Nitrogen was measured by a micro-Kjeldahl method, vacuum distillation being used. The nonprotein nitrogen value was estimated in the Folin-Wu filtrate. The lipid content was estimated by the method of Bloor,<sup>6</sup> with some modifications. Colloid osmotic pressure was measured at 0 C by a modification of the classic membrane bag arrangement of Starling<sup>7</sup> as used by Adair.<sup>8</sup> All determinations were made in duplicate.

#### RESULTS

The condensed results of two typical experiments on one subject are given in the accompanying table. Chart 1 summarizes, in terms of percentage of change, the average results obtained in studies on 6 normal subjects, with whom identical procedures were used.

The most obvious feature in these studies was that the average alterations in four substances—total lipoids, total fatty acids, cholesterol and total protein—were identical within the limits of error. This was true in blood both from the foot and from the arm, but the changes in the blood from the foot were twice as great as those in the blood from the arm.

In our studies the concentrations of all the lipid fractions increased in every instance. The least increase and the greatest disparity between changes in the protein and the lipid occurred in blood from the arm in the second study on subject HB (table). To make a more complete comparison with the results of Man and Peters<sup>4</sup> we performed two studies in which the values for lipid phosphorus and total protein were determined. The concentration of lipid phosphorus in blood from the foot rose 18 and 13.5 per cent as compared with increases in the concentration of protein of 20.9 and 14.7 per cent, respectively.

In 8 cases the concentration of the albumin in the serum was measured separately by the method of Howe.<sup>9</sup> In all cases the con-

6 Bloor, W. R. The Determination of Cholesterol in Blood, *J. Biol. Chem.* **24** 227, 1916.

7 Starling, E. H. On the Absorption of Fluids from the Connective Tissue Spaces, *J. Physiol.* **19** 312, 1896.

8 Adair, G. S. Direct Method of Measuring the Osmotic Pressure of Hemoglobin, *Proc. Roy. Soc., London* **108** 627, 1925.

9 Howe, P. E. The Determination of Proteins in Blood—A Micro Method, *J. Biol. Chem.* **49** 109, 1921.

centration of albumin increased with standing, and the increase was, roughly at least, proportional to the increase in total protein. These results are summarized in chart 2.

It should be noted that, apart from the limitations of the accuracy of the method for albumin, the comparison presented in chart 2 is not a sensitive test for the constancy of the average size of the protein molecules. Since in these studies about two thirds of the total protein is albumin, any changes in albumin would be closely reflected in the total protein concentrations, even if globulin did not participate to the same extent. The results appear in a much less satisfactory light if the indicated changes in globulin are expressed as percentage deviations from the changes in albumin. These values for the same studies, as summarized in chart 2, run as follows: +11, -15, -12.5, +14,

*Summarized Results of Two Experiments on H. B. Showing Alterations in Concentration of the Blood Resulting from a Relatively Upright Posture*

Sample	Standing Time, Min	Angle, Degrees	Oxygen Capacity of Blood, Vol %	Protein Nitrogen, Mg per 100 Cc	Change, %	Total Lipids, Mg per 100 Cc	Change, %	Total Fatty Acids, Mg per 100 Cc	Change, %	Cholesterol, Mg per 100 Cc	Change, %	Colloid Osmotic Pressure, Mm of Water	Change, %
Rest	35	86		1,063		687		431		256		261	
Arm				1,037	+2.5			470	+9.0				
Foot				1,320	+24.0	867	+26.0	532	+35.0	315	+23.0	459	+76
Rest	30	54	21.0	1,057		563		295		263		286	
Arm			22.6	1,174	+11.0	576	+2.0	298	+1.0	287	+7.0	349	+22
Foot			23.6	1,281	+21.0	644	+12.5	335	+13.5	309	+15.5	405	+42

+7.5, -1, +3 and +26.5 per cent. We do not interpret these results as indicating a significant lack of correspondence between changes in the albumin and in the globulin. To us, at least, these results indicate merely the technical limitation of the albumin-globulin method. In a number of studies we have consistently found that analyses in terms of albumin and globulin are inadequate for exacting quantitative studies.

#### COMMENT

It is generally believed that the capillaries are normally impermeable to lipoids (Gardner and Gainsborough,<sup>10</sup> Gaál<sup>11</sup> and Man and Peters<sup>4</sup>). The present results indicate that lipoids are restrained by the capillary wall to the same extent as are the proteins. There remains the question whether this has any consequence on osmosis.

<sup>10</sup> Gardner, J. A., and Gainsborough, H. Cholesterol Secretion in the Urine, *Biochem J* **19** 667, 1925.

<sup>11</sup> Gaál, A. M. Untersuchungen über Cholesterinstoffwechsel, *Ztschr f d ges exper Med* **71** 690, 1930.

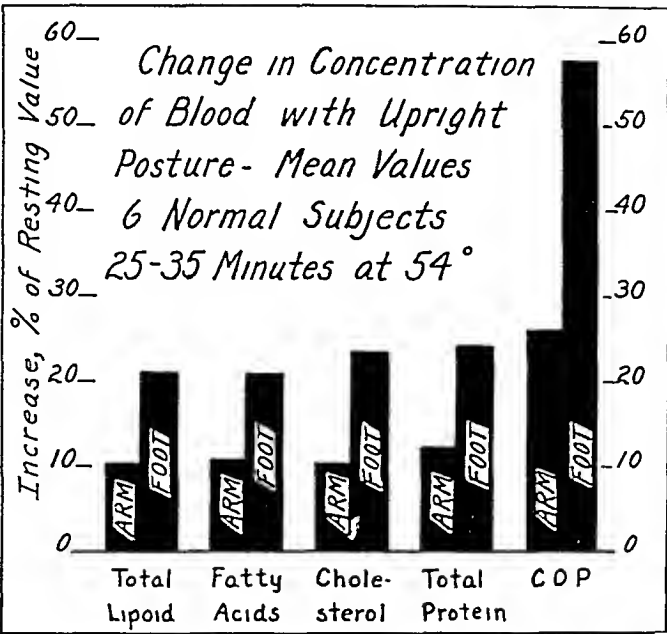


Chart 1—Alterations in the concentration of lipoids and proteins in the blood serum of human beings resulting from an upright posture

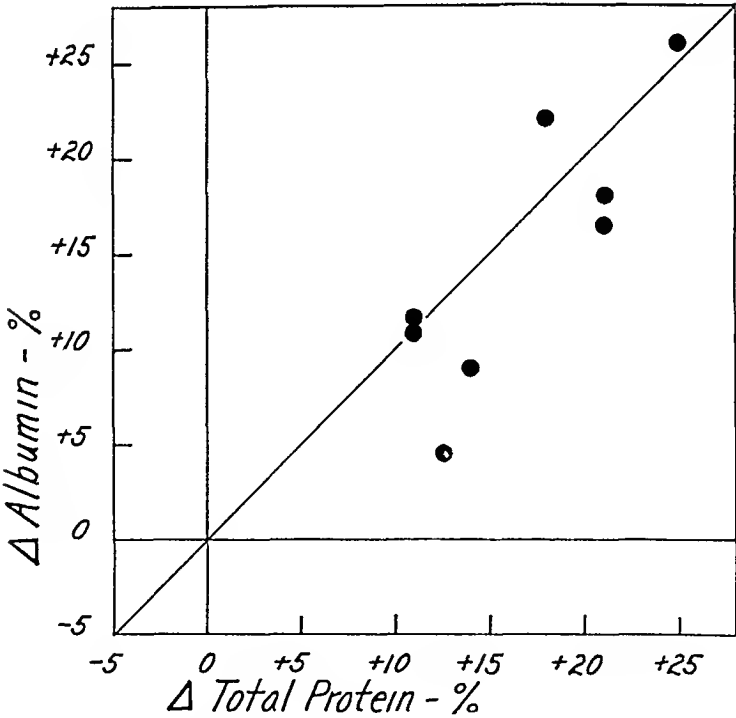


Chart 2—Changes in the concentration of albumin as compared with the concentration of total protein in the blood serum Results of eight experiments on normal human beings at an angle of 54 to 65 degrees from the horizontal for periods of fifteen to thirty minutes

There are indications that some of the lipoids in blood plasma are bound to proteins. Handovsky<sup>12</sup> found that a fourth of the cholesterol in ox serum is firmly bound to globulin. Turner and Gibson<sup>13</sup> reported that about half the plasma lipoids are carried down with the protein precipitate when proteins are salted out of serum. However, at least half the total lipid in blood plasma appears to be "free," i. e., not bound to protein, and the osmotic pressure of this fraction can be estimated for the limiting condition in which the lipoids are molecularly dispersed.

The molecular weight of cholesterol is 386, that of the phospholipoids can be taken as 770 and the average molecular weight for the true fats in blood plasma may be estimated as about 870. In plasma containing 600 mg of total lipoids per hundred cubic centimeters, of which 200 mg represents cholesterol and 200 mg phospholipoids, the molar concentration of the lipoids would be  $\frac{2}{386}$  plus  $\frac{2}{770}$  plus  $\frac{2}{870}$ , or 0.01. The total osmotic pressure of an ideal 0.01 molar solution would be  $0.01 \times 22.4 \times 760 \times 13.5 = 2,300$  mm of water. If it is assumed that as much as half the lipoids are firmly bound to protein, there remains about 1,150 mm of water as the potential osmotic contribution of the lipoids in plasma. Since the total colloid osmotic pressure of normal blood serum is only about 300 to 400 mm of water (that is, about the same as the hydrostatic pressure in the capillaries), it is obvious that not more than a minute fraction of the total lipoids can be osmotically active.

In the present studies the average increase in the total lipid content amounted to 111 mg per hundred cubic centimeters, and the potential osmotic increment, following the foregoing calculation, would amount to about 210 mm of water if all the lipoids were restrained by the membrane and 50 per cent of the lipoids were in a free state of molecular dispersal. As will be shown, the changes in the colloid osmotic pressure with the upright posture agree with the calculations from the protein concentrations within about 5 to 10 mm of water. Accordingly the maximum effect of the lipoids may be put at less than the equivalent of 2 per cent of the molar concentration of the lipoids.

Two other methods for studying the possible effect of lipoids on the colloid osmotic pressure were applied in single experiments. In the first case, ox serum was extracted briefly with cold ether and then dialyzed against a saline buffer until the ether had been removed. At an equivalent concentration of protein the specific colloid osmotic pressure of the serum was not significantly altered, in spite of the fact that the lipid content of the serum was reduced to 69 per cent of the initial concentration. In the second case a sample of lipemic blood serum was centri-

12 Handovsky, H. Untersuchungen über die Zusammensetzung des Blutserums und ihre Bedeutung für Giftwirkungen, *Arch f d ges Physiol* **210** 35, 1925.

13 Turner, M. E., and Gibson, R. B. A Study of the Protein-Lipid Combinations in Blood and Body Fluids. I. Normal Human and Dog Plasma and Horse Serum, *J Clin Investigation* **11** 735, 1932.

fuged, and the uppermost layer, containing a high content of lipid, was removed. This lipid material was dispersed in ten times its volume of ox serum with the aid of a few drops of bile. This artificial lipemic serum was centrifuged, and the top 10 per cent was discarded. The remaining ox serum contained 34 per cent more total lipid than did the original ox serum. In spite of this, the colloid osmotic pressure, at an equivalent concentration of protein, was not significantly altered.

Further studies of this type would be useful, but it seems clear that lipoids do not contribute more than a negligible amount to the colloid osmotic pressure.

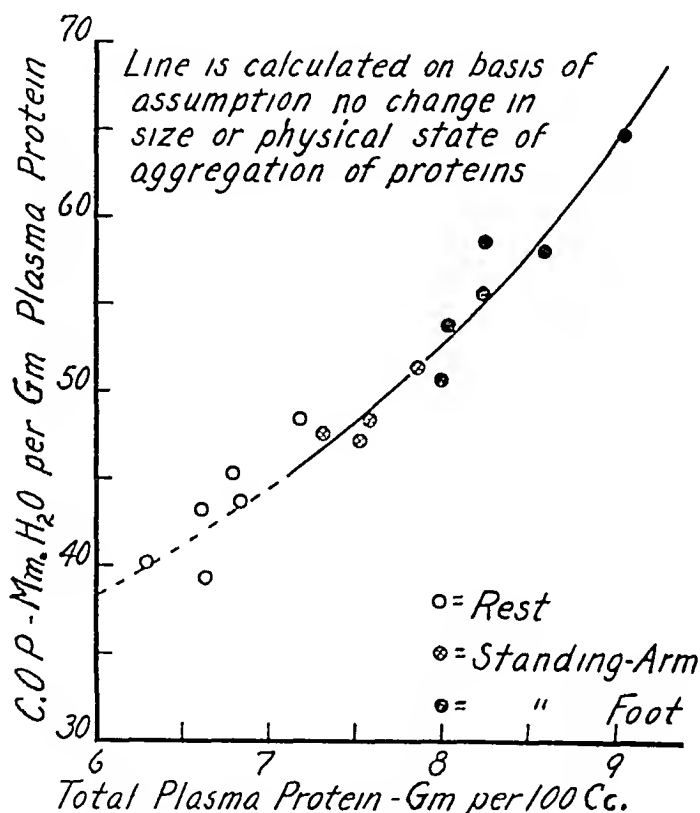


Chart 3—Lack of change in the mean molecular size of the serum proteins when concentrated as a result of quiet standing

The fact remains that the colloid osmotic pressure in the posture experiments increased much more than in proportion to the concentration of protein. A similar disproportionate increase was reported by Youmans and others<sup>3b</sup>. It is well known that the specific osmotic activity of proteins, especially albumin, rises with increasing concentration (Adair and Robinson<sup>14</sup> and Burk<sup>15</sup>). Does this effect account quantitatively for the observed results in the posture experiments?

14 Adair, G. S., and Robinson, M. E. The Analysis of the Osmotic Pressures of the Serum Proteins, and the Molecular Weights of Albumins and Globulins, *Biochem J* **24** 1864, 1930

15 Burk, N. F. Osmotic Pressure, Molecular Weight, and Stability of Serum Albumin, *J Biol Chem* **98** 353, 1932



Osmometric analysis of dilutions of protein solutions has provided a means for calculating the deviation from the predictions of the laws of ideal solutions in blood serum (Keys<sup>16</sup>) The results of such calculations with data from the posture experiments are summarized in chart 3 In this chart the line describes the relation between colloid osmotic pressure and protein concentration, predicted from the observed mean colloid osmotic pressure per gram of protein at the mean protein concentration during the resting state It is assumed, of course, that the change in protein concentration with standing does not involve any alteration in the size or in the state of the protein It is clear that this assumption is fully substantiated by the close relation between theory and observation This can mean only that the change in the protein concentration with standing must find its explanation in one or both of the following processes (1) a loss of fluid from the blood which is free from protein or in which there is a low concentration of proteins, averaging the same in molecular size as the proteins in the plasma, or (2) a gain by the plasma of a mixture of proteins having precisely the same composition as the mixture of proteins originally in the blood plasma The improbability of this last hypothesis should be sufficient to rule it out of consideration

#### SUMMARY

Changes in the concentration of the blood were studied in normal human subjects after they had been for twelve to thirty-five minutes at an angle of 54 degrees from the horizontal Blood was drawn from veins of the arm and foot without stasis

The upright posture resulted in the following average increases in concentration in the serum from the foot total lipid, + 21 per cent, fatty acids, + 21 per cent, cholesterol, + 23 per cent, total protein, + 24 per cent, and colloid osmotic pressure, + 58 per cent Changes in the serum from the arm were closely parallel to those in the serum from the foot but only about half as great Experiments at other angles up to 86 degrees from the horizontal gave similar results

It is shown that the rise in colloid osmotic pressure is quantitatively predictable from the change in concentration of the total proteins, assuming that the mean molecular size of the proteins remains unaltered

Evidence is presented to show that the capillary membranes are as impermeable to lipoids as they are to proteins but that the lipoids exert no colloid osmotic pressure

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16 Keys, A The Study of Colloidal Dimensions, Thermodynamic Activity, and the Mean Molecular Weight of the Mixed Proteins in Blood Serum *J Phys Chem* 42 11, 1938

# Progress in Internal Medicine

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## ALLERGY

A REVIEW OF THE LITERATURE OF 1938

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Each year the papers written on allergy cover a wider territory. What the study of allergy cannot do is being separated little by little from what it can do, and the correlation of such study with internal medicine is improving all the time. Whereas tests for allergy appear to offer a distinct and separate method of diagnosis, they offer, after all, merely one of the methods of determining what is wrong, and the results obtained through such study must still be correlated with the results obtained by other methods.

How does allergy develop? In the answer to this question one should note with Simon<sup>1</sup> the differences between one type of sensitivity, to serum or to poison ivy, for example, which occurs to a greater or lesser extent in all persons exposed to the foreign substance, and the other type, which occurs only in a small number of those exposed. The latter are said to be allergic or atopic, they have a distinct capacity to manifest sensitiveness. This capacity, this atopy, is inherited, its nature is not known.

How does sensitiveness develop? Simon<sup>1</sup> shows that even though typical atopic persons are treated intensively with a foreign protein, like mare's milk or turtle egg, they do not become sensitive to it. If they did, perhaps all of them would become sensitive to all atopogens<sup>1</sup>. In short, it becomes necessary to assume that for each patient a period or periods of predisposition occur and that their occurrence is strictly limited and temporary. What causes them is uncertain. One thinks of infections, of fatigue or of some emotional disturbance, but Simon<sup>1</sup> repeated his experiments with guinea pig serum and turtle egg on children with measles and scarlet fever and yet failed to induce a degree of sensitiveness which was different from that in his controls. Another problem appears.

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<sup>1</sup> Simon, F. A. The Problem of the Development of Hypersensitiveness in Man, *Ann Int Med* **12** 178, 1938

Meantime, Vaughan<sup>2</sup> has stated the belief that alleigy is more common than is appreciated, that all persons are potentially allergic and that the response to harmful environmental change is purposeful but that it varies widely in degree from one person to another. Caulfeild<sup>3</sup> has removed some of the difficulties in correlating anaphylaxis with clinical allergy by showing that the antibodies associated with human hypersensitiveness—the reagins—can be transferred from man to monkey, just as the sensitiveness induced in a guinea pig can be transferred to a monkey's skin. On the practical aspects of allergy there are numerous general articles, the best of which perhaps is a paper by Burrage,<sup>4</sup> who discusses the present day methods of dealing with hay fever and asthma.

In animals the production of sensitiveness depends obviously on the character of the material used and the way in which it is given. Florence Sabin with Joyner<sup>5</sup> has succeeded in producing a cutaneous reaction to tuberculin in guinea pigs without infecting the animals. When old tuberculin is heated, its molecular size is greatly reduced, and in Sabin's opinion this fact explains the previous failures. By injecting intracutaneously in repeated doses a tuberculoprotein precipitated with ammonium sulfate, she succeeded in producing a degree of sensitiveness comparable to that observed in infected animals.

Woods, Burky and Friedenwald<sup>6</sup> worked with tuberculosis in rabbits' eyes. After living tubercle bacilli are inoculated into the groin, sensitiveness of the eye develops at the same time as sensitiveness of the skin, but when bacilli are inoculated into the eye itself, the local sensitiveness develops faster and more intensely. The degree of cutaneous sensitivity becomes a poor measure of the degree of the ocular sensitivity. Perhaps these observations can be applied to the problem presented by the common discrepancy between the severity of symptoms, asthma for example, and the size of the cutaneous reaction.

2 Vaughan, W. T. A Theory Concerning the Mechanism and the Significance of the Allergic Response, *J. Lab. & Clin. Med.* **21** 629, 1936.

3 Caulfeild, A. H. W. The Correlation of Specific Sensitization, as It Occurs Clinically in Man, and as Induced Experimentally in Animals, *Tr. Am. Clin. & Climat. A.* **52** 234, 1936.

4 Burrage, W. S. Relation of Allergy to General Medicine, New England *J. Med.* **217** 551, 1937.

5 Sabin, F. R., and Joyner, A. L. Tubercular Allergy Without Infection, *J. Exper. Med.* **68** 659, 1938.

6 Woods, A. C., Burky, E. L., and Friedenwald, J. S. Experimental Studies of Ocular Tuberculosis. I. Relation of Ocular Sensitivity to Cutaneous Sensitivity in the Systematically Infected Rabbit, *Arch. Ophth.* **19** 229 (Feb.) 1938, II. Relation of Ocular Activity to Ocular Sensitivity in the Normal Rabbit Infected by Injection of Tubercle Bacilli into the Anterior Chamber, *ibid.* **19** 236 (Feb.) 1938, III. Relation of Cutaneous Sensitivity to Ocular Sensitivity in the Normal Rabbit Infected by Injection of Tubercle Bacilli into the Anterior Chamber, *ibid.* **19** 245 (Feb.) 1938.

Another paper by Freund and Opie<sup>7</sup> emphasizes the effectiveness of the skin itself in producing antibodies after intracutaneous injection. Multiple intracutaneous injections are particularly effective in producing both cutaneous sensitiveness (allergy) and antibodies (immunity), although the authors are careful to point out that the two results are not always comparable.

#### ANAPHYLAXIS

One or two papers on experimental anaphylaxis are of particular interest. Davidoff and his co-workers<sup>8</sup> found that sensitized monkeys would react with typical shock even if decerebrated before the second dose. Quill<sup>9</sup> shows that ether anesthesia is not a preventive of anaphylactic shock. Obviously, the phenomenon is a tissue reaction, free from the control of the central nervous system. Heparin sufficient to render the blood of guinea pigs uncoagulable was shown by Doxiades and Lemke<sup>10</sup> not to prevent the ensuing shock.

At the meeting of the Society for the Study of Asthma and Allied conditions in Atlantic City, N. J., in May 1938, Abell, Schenck, Clark and Kern<sup>11</sup> gave an excellent demonstration of the living circulation. The construction, installation and care of a transparent chamber inserted into a rabbit's ear had been developed by Clark and his co-workers, the original technic being described by Abell and Clark<sup>12</sup>. A new paper by Abell and Schenck<sup>13</sup> describes the demonstration of the local reaction in anaphylaxis. Briefly, the method is to punch a hole in the rabbit's ear and then fill the defect with two pieces of thin glass, through which the process of repair can be observed. Arteries, veins and capillaries are seen to grow in to restore the tissue. During anaphylactic shock a series of changes is demonstrable. First the arterioles contract, and the circulation slows. Leukocytes move to the periphery of the flow and adhere to the walls of the blood vessels. Finally, these leukocytes adhere

7 Freund, J., and Opie, E. L. Sensitization and Antibody Formation with Increased Resistance to Tuberculous Infection Induced by Heat-Killed Tubercle Bacilli, *J. Exper. Med.* **68** 273, 1938.

8 Davidoff, L. M., Kopeloff, N., and Kopeloff, L. M. Anaphylaxis in Decerebrated Monkeys, *J. Lab. & Clin. Med.* **23** 30, 1937.

9 Quill, L. M. Anaphylaxis During Ether Anesthesia, *J. A. M. A.* **109** 854 (Sept. 11) 1937.

10 Doxiades, L., and Lemke, H. Beeinflussung des anaphylaktischen Shocks beim Meerschweinchen durch Heparin, *Klin. Wchnschr.* **16** 1061, 1937.

11 Abell, R. G., Schenck, H. P., Clark, E. R., and Kern, R. A. Anaphylaxis. Behaviour of Living Blood Vessels of the Rabbit, demonstrated before the Society for the Study of Asthma and Allied Conditions, Atlantic City, N. J., May 1938.

12 Abell, R. G., and Clark, E. R. Method of Studying the Effects of Chemicals upon Living Cells and Tissues in the Moat Chamber, a Transparent Chamber Inserted in the Rabbit's Ear, *Anat. Rec.* **53** 121, 1932.

13 Abell, R. G., and Schenck, H. P. Microscopic Observations on the Behavior of Living Blood Vessels of the Rabbit During the Reaction of Anaphylaxis, *J. Immunol.* **34** 195, 1938.

to each other, they become heaped up in a mass until eventually the entire flow is occluded by the formation of the plug and then by further contraction of the entire vessel. With the failing blood supply, necrosis sets in, and the Arthus phenomenon becomes well developed. In other words, in rabbit anaphylaxis, death depends on heart failure, which in turn depends on capillary obstructions in the lesser circulation.

Studies on antibodies are interesting. Bronfenbrenner<sup>14</sup> has shown again that rabbits and also mice will react immediately on the simultaneous injection of antigen and antibody and that guinea pigs, too, will react in passive anaphylaxis even if the immune serum is injected simultaneously with the antigen.

Ungar and Parrot<sup>15</sup> made extracts of guinea pigs' lungs and added to one sample Tyrode solution and to another horse serum. These mixtures were then tested on a strip of intestine from a normal guinea pig, the strip being suspended in a bath. In the case of normal lungs the intestine showed no response, but in the case of sensitized lungs the mixture of lung extract and horse serum gave a classic curve, obviously dependent on the reaction of the antibodies in the sensitive tissue.

Passive anaphylaxis may exist long, according to Cohen and Woodruff<sup>16</sup>. Female guinea pigs were sensitized to egg white and four weeks later were shocked with a larger dose. For four months the animals rested and then were bred. The offspring, presumably bearing antibodies and thus sensitized only passively, all reacted to egg white, and 1 died. Some of the female offspring, however, were held without further treatment for six months, and then they in turn were bred. The animals of this third generation were tested, and 5 of 9 reacted. This last finding is a little difficult to understand. Antibodies, whether circulating or fixed, should disappear slowly with time, it is hard to believe that they could be transferred to the third generation. To consider that the small amount of egg white given to the original mother should persist in her own circulation and in that of her offspring to the third generation seems far fetched indeed. If reactions do occur, they must depend on antibodies—on passive anaphylaxis, as the authors state.

#### MECHANISM OF ALLERGY

The mechanism of allergy has been studied from various points of view. The chemical constituents of the blood are easy to investigate.

14 Bronfenbrenner, J. The Allergic State and Its Relation to Hypersensitivity and Resistance, *Am Rev Tuberc* **36** 293, 1937.

15 Ungar, G., and Parrot, J. L. Recherches sur le choc anaphylactique *in vitro*. Mise en liberté d'une substance active par le poumon isolé du cobaye sensibilisé, *Compt rend Soc de biol* **123** 676, 1936.

16 Cohen, M. B., and Woodruff, B. H. Observations on the Transmission of Passive Anaphylactic Sensitivity in the Guinea Pig, *J Allergy* **8** 437, 1937.

*Cholesterol*—The cholesterol content of the serum was studied by Bruger and his associates<sup>17</sup> in Spain's clinic. The patients with hay fever who were doing well under treatment showed cholesterol values that were a little higher than normal, whereas those with asthma showed an average figure that was a little lower. Neither variation was striking. Chobot and Dundy<sup>18</sup> found the cholesterol values about the same for allergic as for nonallergic children. Incidentally, they found that the calcium and phosphorus values were likewise within normal limits for both groups. Bezançon and his associates,<sup>19</sup> in Paris, came to similar conclusions.

*Magnesium*—The magnesium content of the blood was investigated by Braden and Braden Jr.,<sup>20</sup> but the figures for allergic patients were not different from those for the controls.

*Potassium*—An imbalance of potassium is a more interesting possibility, suggested by Rusk and Kenamore<sup>21</sup> in connection with their study of urticaria. Potassium depresses the tactile excitability of the frog's skin. Irritation of the skin leads to a loss of the potassium held in it. Epinephrine increases the potassium content of the blood serum. The effect of potassium salts injected intravenously is similar to the effect of epinephrine. It is possible, the authors think, that potassium is valuable in urticaria—and, I add, in allergy in general. Possibly the good effect of potassium iodide in asthma depends as much on the potassium ion as on the iodine ion. The thought is interesting. Meantime, the authors propose a diet with a high potassium and a low sodium content in the treatment of urticaria.

*Jaundice*—It is said (Hench<sup>22</sup> and Thompson and Wyatt<sup>23</sup>) that jaundice has a favorable effect on the pain and swelling of arthritis. If

17 Bruger, M., Sammis, F. E., Spain, W. C., and Member, S. Serum Cholesterol in Hay Fever and Asthma, *J. Allergy* **9** 551, 1938.

18 Chobot, R., and Dundy, H. D. Serum Cholesterol in Allergy, *J. Allergy* **9** 231, 1938.

19 Bezançon, F., Jacquelin, A., Joly, F., and Guillaumin, C. O. Étude de certains composants chimiques du sang des asthmatiques, *Presse méd.* **44** 2033, 1936.

20 Braden, A. H., and Braden, A. H., Jr. A Study of Blood Magnesium in Allergic Individuals, *South. M. J.* **31** 85, 1938.

21 Rusk, H. A., and Kenamore, B. D. Urticaria. A New Therapeutic Approach, *Ann. Int. Med.* **11** 1838, 1938.

22 Hench, P. S. Effect of Jaundice on Chronic Infectious (Atrophic) Arthritis and on Primary Fibrositis. Further Observations, Attempts to Reproduce the Phenomenon, *Arch. Int. Med.* **61** 451 (March) 1938.

23 Thompson, H. E., and Wyatt, B. L. Experimentally Induced Jaundice (Hyperbilirubinemia). Report of Animal Experimentation and of the Physiologic Effect of Jaundice in Patients with Atrophic Arthritis, *Arch. Int. Med.* **61** 481 (March) 1938.

this observation can be confirmed, it becomes of considerable interest, and one would like to transfer the idea to the subject of allergy. Unfortunately, however, jaundice appears to be rare in allergy, and one wonders whether some definite antagonism may exist. The question should be borne in mind, for a positive finding might lead to a useful therapeutic method.

*Adrenal Cortex*—Two years ago considerable interest in the relation of the adrenal cortex to asthma was aroused. Now comes a paper by Prickman and Koelsche<sup>24</sup> in which they report treating patients with asthma with adrenal cortex extract intravenously, giving large amounts supplemented by large doses of sodium chloride by mouth. However, little or no benefit resulted.

*Vitamin C*—Ascorbic acid is receiving more attention, but neither in asthma (Hunt<sup>25</sup>) nor in anaphylaxis (Eyer and his associates<sup>26</sup>) could it be shown that treatment with it had any effect on the clinical process. On the other hand, Rosenberg<sup>27</sup> found 7 patients with urticaria who were receiving a diet without fruits and apparently deficient in vitamin C. With the addition of oranges and lemons, the lesions subsided. In rheumatoid arthritis and in rheumatic fever Rinehart and associates<sup>28</sup> studied the ascorbic acid level and found it lowered in both conditions and were encouraged by their preliminary good results after feeding the vitamin in high doses to their patients.

*Histamine*—Histamine and analogous substances concerned with the activity of the autonomic nervous system seem to me to be of considerable theoretic importance in allergy for several reasons. First, a constant symptom (asthma) is produced by a wide variety of exciting causes. Second, the patients wheeze, but also they are sick. Their blood pressure is low, they sweat, they cannot eat. They are utterly miserable. They seem to be poisoned by something which causes "overflow symptoms" in addition to asthma. Finally, in animals the injection of histamine produces a train of symptoms entirely comparable to those of anaphylactic shock. It is important to think of histamine carefully.

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24 Prickman, L. E., and Koelsche, G. A. Observations on the Treatment of Asthma and Related Conditions with Suprarenal Cortical Extract (Cortin), *J Allergy* **9** 158, 1938.

25 Hunt, H. B. Ascorbic Acid in Bronchial Asthma. Report of Therapeutic Trial on Twenty-Five Cases, *Brit. M. J.* **1** 726, 1938.

26 Eyer, S. W., Dragstedt, C. A., and Ramirez de Arellano, M. Vitamin C and Anaphylactic Shock in Dogs, *Proc. Soc. Exper. Biol. & Med.* **38** 642, 1938.

27 Rosenberg, W. A. Vitamin C Deficiency as a Cause of Urticaria, *Arch. Dermat. & Syph.* **37** 1010 (June) 1938.

28 Rinehart, J. F., Greenberg, L. D., Baker, F., Mettler, S. R., and Bruckman, F. Metabolism of Vitamin C in Rheumatoid Arthritis, *Arch. Int. Med.* **61** 537 (April) 1938. Rinehart, J. F., Greenberg, L. D., Olney, M. B., and Choy, F. Metabolism of Vitamin C in Rheumatic Fever, *ibid.* **61** 552 (April) 1938.

Last summer the Theobald Smith Medal was awarded to a young man, Dr Charles F. Code, of the Mayo Foundation. He had worked on the content of histamine in the blood, improving the method of estimation.<sup>29</sup> He showed that when fresh blood is centrifuged, the histamine is found to be mostly in the cells. The plasma contains little. When, however, the blood clots, most of the histamine appears in the serum. By a process of differential centrifugation, the histamine activity was found to be mostly in the white cells. Finally, by working with special types of blood from patients with leukemia and material from abscesses of different kinds in animals, Code found that histamine was associated particularly with the eosinophilic cells. The last finding opens a practical aspect which obviously needs much further study. Whether or not the total histamine content of the blood is increased in asthma is not yet known. Riesser's<sup>30</sup> figures were the same for the bloods of asthmatic and tuberculous patients. On the other hand, Fiessinger and his associates<sup>31</sup> found more histamine in the blood in cases of urticaria and asthma than in cases of other conditions, notably psoriasis. The skin, however, seems to contain a considerable amount of histamine. Riesser<sup>30</sup> found that the local lesion of the Atthus phenomenon contained from four to ten times as much histamine as normal, as expected perhaps because of the high leukocyte content. Tarras<sup>32</sup> observed that in arspenamine dermatitis the blood contained much more histamine than normal.

*Acetylcholine* —Acetylcholine has an action much like that of histamine, but it differs in two important respects, as has been recently reviewed by Kokas, Sarkady and Went.<sup>33</sup> First, the substance is extremely labile, losing its toxicity rapidly and easily. Second, the action of acetylcholine is blocked promptly and completely by small quantities of atropine. To determine the acetylcholine content of the blood is therefore a difficult technical procedure. It is much easier to determine

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29 Code, C. F. The Quantitative Estimation of Histamine in the Blood, *J. Physiol.* **89** 257, 1937, The Source in Blood of the Histamine-Like Constituent, *ibid.* **90** 349, 1937, The Histamine-Like Activity of White Blood Cells, *ibid.* **90** 485, 1937. Code, C. F., and Ing, H. R. Isolation of Histamine from the White Cell Layer of Centrifuged Rabbit Blood, *ibid.* **90** 501, 1937.

30 Riesser, O. Histaminstudien, *Arch. f. exper. Path. u. Pharmacol.* **187** 1, 1937.

31 Fiessinger, N., Gajdos, A., and Panayotopoulos, E. L'histaminémie chez les cirrhotiques et dans les maladies hyperergiques, *Bull. et mém. Soc. méd. d'hôp. de Paris* **54** 500, 1938.

32 Tarras-Wahlberg, B. The Histamine Content of the Blood in Salvarsan Dermatitis, *Acta dermat.-venereol.* **18** 284, 1937.

33 Kokas, F., Sarkady, L., and Went, S. Ueber die Rolle von Cholin und Histamin im Entstehungsmechanismus anaphylaktischer Schockerscheinungen, *Arch. f. exper. Path. u. Pharmacol.* **187** 479, 1937.



the amount of acetylcholine indirectly by determining the amount of that ferment which under normal conditions causes its destruction. The choline esterase activity of the blood serum can be determined without too much difficulty. Milhorat<sup>34</sup> studied a variety of patients, including 5 with asthma, but found that for them the values for choline esterase varied widely from high to low.

Histamine and perhaps acetylcholine at the same time are liberated from many tissues under different conditions. In three papers Feldberg and various associates<sup>35</sup> showed that when the lungs were perfused with a dilute salt solution to which snake venom, staphylococcus toxin or peptone was added, the perfusate contained much histamine, which arose presumably as a result of the tissue injury, just as Feldberg and Kraye<sup>36</sup> had shown previously that electrical stimulation of the vagus nerve caused an acetylcholine-like substance to appear in the blood.

The question of treatment with histamine, in the hope of increasing the resistance to it, has been raised again. Kokas<sup>33</sup> injected into dogs small doses daily for fifteen days but nevertheless found that these animals could be shocked as easily as untreated animals. Mead and his associates<sup>37</sup> have shown previously that peptone shock does not protect against anaphylactic shock and that desensitization is therefore not due to histamine exhaustion.

*Emotional Factor* —Meantime, and in addition to objective findings of many kinds, every clinician knows that the emotional factor is always important in allergy. Strauss<sup>38</sup> studied 30 patients with asthma from the psychogenic point of view and found that a nervous element was strongly present in 16 of them and definite in 9 others. An excellent discussion of the subject was given by Eyermann<sup>39</sup> in his presidential address before the Association for the Study of Allergy. The subject

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34 Milhorat, A. T. The Choline-Esterase Activity of the Blood Serum in Disease, *J. Clin. Investigation* **17** 649, 1938.

35 Feldberg, W., and Kellaway, C. H. The Liberation of Histamine from the Perfused Lung by Snake Venoms, *J. Physiol.* **90** 257, 1937, The Liberation of Histamine from the Perfused Lung by Staphylococcal Toxin, *ibid.* **90** 280, 1937, The Liberation of Histamine from the Perfused Lung by Peptone, *ibid.* **90** 288, 1937.

36 Feldberg, W., and Kraye, O. Das Auftreten eines azetylcholinartigen Stoffes im Herzvenenblut von Warmblutern bei Reizung der Nervi Vagi, *Arch. f. exper. Path. u. Pharmacol.* **172** 170, 1933.

37 Mead, F. B., Dragstedt, C. A., and Eyer, S. W. Relationship Between Peptone Shock and Anaphylactic Shock, *Proc. Soc. Exper. Biol. & Med.* **37** 8, 1937.

38 Strauss, E. B. Psychogenic Factor in Asthma, *Guy's Hosp. Rep.* **87** 273, 1937.

39 Eyermann, C. H. The Emotional Component of Bronchial Asthma, *J. Allergy* **9** 565, 1938.

of psychology in allergy is introduced at this point because of the possibility that the effect of emotions can be explained by some change in the hormones—an ultimate effect which is comparable to that of chemical or mechanical injury

#### SERUM DISEASE

Cohen <sup>40</sup> reports the following case. A boy was kicked by a horse and was given antitetanus serum in two doses on successive days. On the sixth day he had fever and generalized urticaria and on the seventh day pain in the neck and limbs as well as trismus. A diagnosis of tetanus was made, and more antitoxin was given, this time intravenously. During the injection a typical anaphylactic shock occurred, the temperature rose to 106 F and the situation became desperate. Ten hours later there was observed at the site of the venipuncture a bluish red, sharply demarcated area that was indurated and painful. For three days the boy was at the point of death. There was complete suppression of urine, and meantime the area in the arm became gangrenous and the basilic vein thrombosed. Slowly, however, he improved, until suddenly, on the tenth day, he died, presumably because of an embolus.

Such a typical Arthus phenomenon would have been prevented if the symptoms of the original serum disease had been better understood. The subject is always important and always worthy of emphasis and of repetition.

The new knowledge concerning the production of active immunity to tetanus is of direct value, and I, for one, believe that all patients, particularly children who are sensitive to horse serum, should be given the benefit of treatment with tetanus toxoid to produce active immunity, thus all fear of tetanus would be abolished when wounds or injuries are incurred. Studies by Gold <sup>41</sup> and by Jones and Moss <sup>42</sup> give the details. Apparently the concentration of demonstrable antibodies which follows the first series of doses is not always impressive, but when an additional small dose is given much later, this small supplementary treatment seems to produce a great effect and to stimulate the production of antitoxin in quantity.

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40 Cohen, M. B. The Importance of the Recognition of Serum Disease. *Ohio State M. J.* **32** 225, 1936.

41 Gold, H. Studies on Tetanus Toxoid. Active Immunization of Normal Persons with Tetanus Toxoid, Alum Precipitated, Refined, *J. A. M. A.* **109** 481 (Aug. 14) 1937, Studies on Tetanus Toxoid. Active Immunization of Allergic Persons with Tetanus Toxoid, Alum Precipitated, Refined, *J. Allergy* **8** 230, 1937.

42 Jones, F. G., and Moss, J. M. Studies on Tetanus Toxoid. II. The Response of Human Subjects to an Injection of Tetanus Toxoid or Tetanus Alum Precipitated Toxoid One Year After Immunization, *J. Immunol.* **33** 183 1937.

The diagnosis of horse serum sensitiveness is not easy. Whether the cutaneous test can provide an accurate index has been disputed by numerous workers. Davis<sup>43</sup> applied a cutaneous test with horse serum to children with measles and scarlet fever. Of the 150 patients who had not previously received injections of horse serum, 30 per cent gave mild reactions, whereas of the 100 patients who had had serum previously, 88 per cent reacted. Diphtheria antitoxin was given to both groups, and two or three weeks later all reacted to the horse serum test. In another group Davis noted that 61 per cent gave no cutaneous reaction to horse serum, yet 22.1 per cent had serum disease after antitoxin was administered, whereas of the 39 per cent who showed cutaneous sensitivity at the start, 28.2 per cent had a serum reaction—a figure which was higher perhaps but not nearly so high as expected. The author concluded that the reaction to the cutaneous test as an index of the degree of sensitiveness had little real value.

Nerve lesions, as a special form of serum disease, may sometimes follow an injection of foreign serum. The complication is rare, but it does occur and should be borne in mind. Brahdý<sup>44</sup> describes paralysis of the musculospiral nerve following a dose of tetanus antitoxin.

#### HAY FEVER

Pollen surveys are being made all over the world. From Melbourne comes the report of Sharwood,<sup>45</sup> showing the great importance of grass pollens between October and January, evidently the same kind of grasses as found in America. He lays stress on plantain. The tree pollens are likewise important, and it is curious that the season occurs in August and September, relatively much earlier than for American trees (April and May). Elm, plane, pine and oak are mentioned.

Argentina is surveyed by Bozzola.<sup>46</sup> In the United States Sylvester and Durham<sup>47</sup> show that ragweed may be as important in the vicinity of the larger cities in Maine as it is elsewhere.

Oral therapy of hay fever by feeding doses of pollen or pollen extract is an important topic, and other reports on it have been made. Bernstein and Feinberg<sup>48</sup> tried to correlate the proper dose with the

43 Davis, H. M. Horse-Serum Skin Tests, *J Hyg* **38** 325, 1938.

44 Brahdý, L. Musculo-Spiral Paralysis After Serum Injection Recurring After Second Injection, *Ann Int Med* **11** 1911, 1938.

45 Sharwood, M. M. Further Studies of the Pollen Content of the Melbourne Air, *M J Australia* **1** 117, 1937.

46 Bozzola, J. A. Contribucion al estudio de la flora anemofila alergogena argentina, *Semana méd* **1** 1196, 1937.

47 Sylvester, C. B., and Durham, O. C. Ragweed Pollen Survey in Maine for 1937, *New England J Med* **219** 428, 1938.

48 Bernstein, T. B., and Feinberg, S. M. Oral Ragweed Pollen Therapy. Clinical Results of Experiments on Gastrointestinal Absorption, *Arch Int Med* **62** 297 (Aug) 1938.

degree of the patient's sensitiveness. They sought to determine the amount of pollen which when given by mouth would elicit a reaction in the arm of a normal person at the sites which had previously been sensitized by an intracutaneous injection of hay fever serum. Some of the normal recipients were given several grams of pollen at a time, but only 1 of 17 showed any response in the passively sensitized area. However, each recipient reacted promptly when the usual moderate quantity was injected under the skin. Evidently the risk of disturbances due to gastrointestinal absorption is small. Twenty patients sensitive to ragweed were treated with relatively enormous doses of ragweed pollen by mouth. Only 2 showed moderate improvement. The others derived no benefit, and 6 of them showed mild gastric disturbances with colicky pains and nausea after the doses. Bohner's<sup>49</sup> report is a little more enthusiastic. He too fed ragweed pollen in large quantities. Of 21 patients, 13 were relieved by oral therapy, as compared with 16 of another group of 21 patients who were relieved by subcutaneous treatment. The question of oral therapy is still open.

New studies of pollen extracts include that of Long and Teller,<sup>50</sup> who observed that ultrafiltration removes a good deal of the active substance, as does also absorption with protein or zinc hydroxide. Naterman<sup>51</sup> suggests that pollen extracts be emulsified in oil so that there will be slower absorption of the active principle and thus general reactions will be prevented and larger total doses may be given. In preliminary studies he showed that when phenolphthalein is emulsified and suspended in oil according to his method, the curve of its excretion in the urine after injection becomes almost a straight line, in place of the usual peak. Theoretically the method is good, and among 17 of Naterman's patients the results were excellent in 5 and good in 10. My colleagues and I have also used this method but unfortunately have observed that some doses produced local irritative reactions which were unpleasant. How common this difficulty may be and whether it can be overcome remain to be seen.

The specificity of pollen is always important. Grubb and Vaughan<sup>52</sup> have surveyed their clinical material but conclude that no single pollen is representative of any entire group. In this connection it is interesting

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49 Bohner, C. B. Treatment of Ragweed Pollenosis. Comparison of Oral and Hypodermic Medication, *J. Indiana M. A.* **31** 279, 1938.

50 Long, W. L., and Teller, I. Activation of Ultrafiltrates of Ragweed Pollen Extracts by Means of Colloidal Substances. *J. Allergy* **9** 433, 1938.

51 Naterman, H. L. The Treatment of Hay Fever by Injections of Pollen Extract Emulsified in Lanolin and Olive Oil. Preliminary Report, *New England J. Med.* **218** 797, 1938.

52 Grubb, G. D., and Vaughan, W. T. Evidence of Group Specific and Species Specific Sensitization of Pollens, *J. Allergy* **9** 211, 1938.

that in England, Freeman and Hughes<sup>53</sup> found that only 3 of 100 persons sensitive to timothy failed to give a positive cutaneous reaction to the pollen of sugar cane, which none of them had ever seen

The absorption of pollen, as indeed of other dusts, is an important item in the study of the production of pollen asthma, which, incidentally occurs frequently, whereas involvement of the larynx occurs almost never Joffey and Drinker<sup>54</sup> have studied the absorption of dyes from the nose and pharynx of various animals If the cervical lymph nodes are dissected free, the blue dye will be seen to appear in them within a few minutes—promptly in the cat, monkey and rabbit and more slowly in the dog In some contrast suspensions of graphite, with particles of larger size, did not penetrate to the lymph vessels The paper is of practical interest, for it confirms the clinical impression that inhaled pollen reaches the lungs not directly but through the lymphatic ducts and the blood stream

#### PATHOLOGY OF ASTHMA

The pathology of asthma is a topic closely related to the study of the mechanism It is generally agreed that when a patient dies in an attack of asthma and from no other cause, the lesion consists essentially of tough, sticky plugs which occlude the lumen of almost all the medium-sized and smaller bronchi Death results from asphyxiation New cases are reported by Wiseman<sup>55</sup> and by Thieme and Sheldon<sup>56</sup>

The pathologic complications of asthma are receiving more attention Periarthritis nodosa is a disease which may be related in some way to asthma and allergy, partly because it has been found to develop in several asthmatic patients and partly because eosinophilia of high degree is one of its characteristics The literature on the subject has been reviewed in two excellent articles, both published in 1936, one by Motley<sup>57</sup> and the other by Cohen, Kline and Young<sup>58</sup> Now a new case is reported by Berger and Weitz,<sup>59</sup> who made the diagnosis ante mortem

53 Freeman, J, and Hughes, W H Biological Polyvalency of Antigens, with Special Reference to Hay Fever, *Lancet* **1** 941, 1938

54 Joffey, J M, and Drinker, C K The Lymphatic Pathway from the Nose and Pharynx The Absorption of Dyes, *J Exper Med* **68** 629, 1938

55 Wiseman, J R Report of a Case of Status Asthmaticus with Autopsy, *Ann Int Med* **11** 212, 1937

56 Thieme, E T, and Sheldon, J M A Correlation of the Clinical and Pathologic Findings in Bronchial Asthma, *J Allergy* **9** 246, 1938

57 Motley, L Periarthritis Nodosa, with Report of a Case Showing Unusual Features and Apparent Recovery, *J A M A* **106** 898 (March 14) 1936

58 Cohen, M B, Kline, B S, and Young, A M The Clinical Diagnosis of Periarthritis Nodosa, *J A M A* **107** 1555 (Nov 7) 1936

59 Berger, S S, and Weitz, M A Periarthritis Nodosa, Case Report, *J Allergy* **9** 489, 1938

and confirmed it by biopsy of muscle. Another case is reported by Sandler,<sup>60</sup> who found 55 per cent eosinophils on one occasion. Somewhat related is pulmonary arteriolar sclerosis, discussed now by Kaump and Dry,<sup>61</sup> who observed the lesions post mortem and found that in only half the cases were symptoms of disease of the respiratory tract recognized clinically. Another report is that of Rothschild and Goldbloom,<sup>62</sup> who describe the case of a man aged 33 who died with what appeared to be coronary thrombosis, but autopsy showed changes in the arteries of the lungs rather than of the heart.

Subcutaneous emphysema with spontaneous pneumothorax is a direct complication of the dyspnea in asthma. Cases are reported by Elliott<sup>63</sup> and by the Rosenbergs.<sup>64</sup>

#### THE TREATMENT OF ASTHMA

There are several new suggestions regarding therapy. Keeney,<sup>65</sup> in Gay's clinic at Baltimore, has described an epinephrine preparation which is slowly absorbed—a suspension of powdered epinephrine in oil. With this preparation remarkable results were obtained in the control of asthmatic symptoms. The oil medium provides for slow absorption and, thus, for a marked prolongation of the effect of the epinephrine. In our hands, however, the results have not been so brilliant, and, unfortunately, we have observed that in 1 or 2 instances the subcutaneous doses were accompanied by somewhat severe local reactions. Perhaps, however, after modifications of the oily preparation have been made it will prove to be much more satisfactory. Certainly the idea behind the method is a good one.

Hypertonic solutions of dextrose and sucrose to be given intravenously have been recommended. Keeney<sup>66</sup> has given as much as

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60 Sandler, E. J. Periarthritis Nodosa. A Report of a Case Diagnosed Clinically and Confirmed by Necropsy, *Am J M Sc* **195** 794, 1938.

61 Kaump, D. H., and Dry, T. J. Pulmonary Arteriolar Sclerosis. A Clinicopathologic Study, *Arch Int Med* **61** 1 (Jan.) 1938.

62 Rothschild, M. A., and Goldbloom, A. A. Clinical Studies in Circulatory Adjustments. IV. Obliterating Pulmonary Arteritis with Secondary Pulmonary Changes and Right Ventricular Hypertrophy, Report of a Case with Autopsy, *Arch Int Med* **61** 600 (April) 1938.

63 Elliott, R. W. Subcutaneous Emphysema and Pneumothorax in Bronchial Asthma, *Lancet* **1** 1104, 1938.

64 Rosenberg, L., and Rosenberg, J. Subcutaneous Emphysema Complicating Bronchial Asthma. Report of a Case and an Analysis of Seventeen Previously Reported Cases, *Am J M Sc* **195** 682, 1938.

65 Keeney, E. L. A Slowly Absorbed Epinephrine Preparation. Preliminary Report, *Bull Johns Hopkins Hosp* **62** 227, 1938.

66 Keeney, E. L. The Effectiveness of Intravenous Hypertonic Sucrose and Adrenalin in the Treatment of Status Asthmaticus, *J Allergy* **9** 497, 1938.

100 cc of 50 per cent solution of sucrose, producing prompt relief of the asthmatic attack. He has given as many as twelve doses to the same patient. Stoesser and Cook<sup>67</sup> used 25 per cent solution of dextrose, giving 150 to 200 cc intravenously to 3 children with success.

Theophylline with ethylenediamine (aminophylline) is a purin compound the action of which is to improve capillary blood flow and cause diuresis. For several years it has been used in cardiorenal disease with good results, and now it has been tried in asthma. Three recent reports indicate that the drug is a useful addition to the methods of treatment. The dose varies from 3 to 7½ grams (0.19 to 0.48 Gm) dissolved in 10 cc of saline solution and is to be given intravenously for severe attacks. The details are reported in papers by Schmidt,<sup>68</sup> Herrmann and Aynesworth<sup>69</sup> and Greene, Paul and Feller.<sup>70</sup>

In allergic cutaneous disease and in epilepsy, migraine and urticaria Wendt<sup>71</sup> (1937) and Klein<sup>72</sup> (1938) have suggested the use of sodium thiosulfate ( $\text{Na}_2\text{S}_2\text{O}_3 + 5\text{H}_2\text{O}$ ), 1 Gm of the drug to be dissolved in a 10 cc ampule and given intravenously on each of three successive days. So far we have had no experience with it.

Benzedrine has a pharmacologic action closely similar to that of epinephrine, and it is therefore not surprising to have Swineford<sup>73</sup> claim that inhalation of benzedrine is helpful in asthma.

Bronchoscopic examination and treatment may be life saving. Andrews<sup>74</sup> reviews the objects to study the bronchial mucous membrane, to aspirate the secretions and so to prevent the development of local areas of collapse in the pulmonary tissue. The method is not new,

67 Stoesser, A. V., and Cook, M. M. Hypertonic Dextrose Solutions in Treatment of Bronchial Asthma, *Journal-Lancet* **58** 12, 1938.

68 Schmidt, F. Zur Purinkörperbehandlung des Asthma bronchiale, *Med Welt* **11** 1530, 1937.

69 Herrmann, G., and Aynesworth, M. B. Successful Treatment of Persistent Extreme Dyspnoea, "Status Asthmaticus" Use of Theophylline Ethylene Diamine (Aminophylline U. S. P.) Intravenously, *J. Lab. & Clin. Med.* **23** 135, 1937.

70 Greene, J. A., Paul, W. D., and Feller, A. E. The Action of Theophylline with Ethylenediamine on Intrathecal and Venous Pressures in Cardiac Failure and on Bronchial Obstruction in Cardiac Failure and in Bronchial Asthma, *J. A. M. A.* **109** 1712 (Nov 20) 1937.

71 Wendt, H. Ueber entgiftende und antiallergische Wirkung des Natriumthiosulfat, *Deutsche med. Wchnschr.* **63** 1832, 1937.

72 Klein, J. E. Sodium Thiosulphate in the Treatment of Allergy. Report of Six Cases, *Arch. Pediat.* **55** 197, 1938.

73 Swineford, O., Jr. Intrapulmonary Inhalation of Benzedrine, *J. Allergy* **9** 572, 1938.

74 Andrews, A. H., Jr. Bronchoscopy in Bronchial Asthma, *Illinois M. J.* **73** 25, 1938.

but it is good to hear that the results were favorable in 75 per cent of 235 cases. Related to the bronchoscopic method is the use of iodized poppyseed oil, which appears to be gaining in general favor. If the throat can be well cocainized, so that the gag reflex is prevented, it is easy literally to pour the oil slowly down the trachea while the patient is instructed to keep breathing in short, rapid pants. In some cases the procedure is followed by real improvement in the symptoms, so that for several weeks afterward the cough is less and the tendency to spasm is much less. One difficulty has been the fear of trouble from the retention of oil in the lungs. That this fear has been justified is shown in 2 cases reported by Flamm<sup>75</sup>. In each of them temporary improvement was followed by an increase of symptoms, which were worse than ever. Apparently the iodized oil had acted as a true foreign body.

When the asthmatic patient reaches a desperate state, "status asthmaticus," almost any procedure is worth trying. Kahn<sup>76</sup> lays stress on the use of ether and olive oil by rectum. He mixes the drugs together in equal parts and injects from 5 to 7 ounces (150 to 200 cc) of the mixture into the rectum. The general anesthesia which results is almost complete, and in 4 of his 10 cases relief was obtained from severe attacks. A good paper on this and other emergency treatment is that of Waldbott<sup>77</sup>. More drastic is the report by Rienhoff and Gay,<sup>78</sup> who submitted 11 patients to the operation of bilateral resection of the posterior pulmonary plexus. Four patients were rendered completely free from attacks, and 5 others were greatly improved. One died, and 1 was not benefited.

#### FUNGI AND OTHER ALLERGENS

Durham<sup>79</sup> presents the latest figures on the incidence of air-borne fungous spores. *Alternaria* occurs widely, all over the country. It occurs throughout the summer season. Indeed, it appears in the air before the trees bloom in spring, and it continues until after the ragweed fades in the fall. Schonwald<sup>80</sup> also finds that air-borne mold spores are

75 Flamm, G. Retention of Lipiodol in the Lungs, *J. Allergy* **9** 593, 1938.

76 Kahn, I. S. Status Asthmaticus. Report of Sixteen Cases, *J. Allergy* **8** 158, 1937.

77 Waldbott, G. L. Emergency Treatment in Asthma (Asthmatic Crisis), *J. A. M. A.* **110** 1423 (April 30) 1938.

78 Rienhoff, W. F., Jr., and Gay, L. N. Treatment of Intractable Bronchial Asthma by Bilateral Resection of Posterior Pulmonary Plexus, *Arch. Surg.* **37** 456 (Sept.) 1938.

79 Durham, O. C. The Incidence of Air-Borne Fungus Spores. I. *Alternaria*, *J. Allergy* **8** 480, 1937.

80 Schonwald, P. Allergenic Molds in the Pacific Northwest, *J. Allergy* **9** 175, 1938.



common in the atmosphere of the Pacific Northwest. Many of his patients give positive reactions to the corresponding extracts, and treatment with mold extracts gives helpful improvement. Harris<sup>81</sup> describes 12 patients who were sensitive to both pollens and molds. They were greatly improved when molds were given. Somewhat related is the report by Metzger<sup>82</sup> on Spanish moss (*Dendropogon usneoides*), which hangs over the live oak trees in the cotton states. He made cutaneous tests with extracts of the pollen of the moss flowers, of the scales from the dried moss and of the vegetable fibers, but none of these materials produced positive reactions. Evidently Spanish moss is not important.

Jute is another vegetable fiber which, like kapok, ought to be a good pabulum for the growth of molds and therefore ought to have allergenic properties. Stevens and Jordan<sup>83</sup> report the facts regarding 5 patients who were sensitive to jute.

Bees evidently give off some sort of volatile dust substance comparable to that from flies, for Foister<sup>84</sup> describes the coryza and asthma which sometimes occur in those who raise bees.

#### CUTANEOUS TESTS

There is more evidence of the discrepancy between the cutaneous tests and symptoms. Rynes<sup>85</sup> studied 367 patients whose skin was sensitive to various animal danders and found that only 24 per cent were aware that animals had anything to do with their disorders. After study it was found that contacts with animals produced symptoms as follows: contact with cats in 18 per cent, with horses in 62 per cent and with dogs in 20 per cent. The results of treatment, both by elimination and by desensitization, for the group as a whole were—good in 46 per cent, fair in 41 per cent and poor in 13 per cent, that is to say, satisfactory results were obtained in 87 per cent of the cases. However, some of the patients were followed for only a few months.

Swineford and Grove<sup>86</sup> were curious to see whether epinephrine injected just before the cutaneous tests would affect the results. They

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81 Harris, L. H. Molds as Cause of Allergy, *Ohio State M. J.* **34** 158, 1938.

82 Metzger, F. C. Spanish Moss (*Dendropogon Usneoides*), *J. Florida M. A.* **24** 99, 1937.

83 Stevens, F. A., and Jordan, L. Sensitization to Jute, *J. Allergy* **9** 610, 1938.

84 Forster, K. A. Ueber eine interessante Beobachtung bei Bienengift-Arbeiterinnen, *Arch. f. Gewerbepath. u. Gewerbehyg.* **8** 117, 1937.

85 Rynes, S. E. A Critical Analysis of Animal Dander Reactions, *J. Allergy* **8** 470, 1937.

86 Swineford, O., Jr., and Grove, P. T. Effects of Adrenalin on Skin Reactions, *J. Allergy* **8** 475, 1937.

found that there was a slight diminution in fifteen to thirty minutes, but after an hour no effect could be demonstrable

Dorfman and Efron<sup>87</sup> studied cutaneous tests with serial dilutions of house dust and Bermuda grass, finding that with increasing concentrations the size of the local response becomes relatively uniform. Cutaneous tests are not a good measure of antigenic activity. However, my experience is that the least dilution which will provide a local reaction does provide a measure of antigenic activity and that decreasing concentrations do constitute a valuable index.

#### ALLERGY OF THE SKIN

*Atopic Eczema*—Atopic eczema, which has a mechanism like that of hay fever and asthma, is common in infants. Hill<sup>88</sup> has studied a large series of patients and has found that even before the age of 3 months positive cutaneous reactions to cow's milk proteins can be obtained with the intracutaneous method. However, the eczema in these children did not always improve when they were placed on a milk-free diet, the reason being that some of them were given goat's milk, which the author thinks contains a chemical fraction common to that of cow's milk. The casein portions of the two kinds of milk appear to be similar.

*Industrial Dermatitis*—Industrial dermatitis presents a problem which is related both to atopic eczema and to contact dermatitis, and those interested in the subject should read the symposium which appeared in *The Journal of the American Medical Association* in Oct 22, 1938. As Sulzberger<sup>89</sup> points out so well, there are always two factors: first, there is the inherent capacity of the individual to acquire sensitiveness, and, second, there is the industrial exposure. For the latter, the responsibility may rest with the company, but for the former the company can hardly be held. In each case the physician should be ready to say with some assurance whether the dermatitis is, in all probability, to a major degree dependent on the patient's exposure or whether it is not so dependent, or, finally, if he cannot decide, then he should say so.

*Contact Dermatitis*—Contact dermatitis is not uncommon. Cases of dermatitis due to pollen are classic. A patient with typical ragweed

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87 Dorfman, R. I., and Efron, B. G. Studies with Antigens. I. The Skin Reaction Curve Obtained with Serial Dilutions of Extracts, *J. Allergy* **9** 464, 1938.

88 Hill, L. W. Sensitivity to Cow's Milk in Infantile Eczema, *J. Pediatr.* **12** 725, 1938.

89 Sulzberger, M. B., and Finnerud, C. W. Industrial Dermatitis. Definitions and Criteria for Diagnosis, *J. A. M. A.* **111** 1528 (Oct 22) 1938.

dermatitis is reported on by Rudolph and Deutsch<sup>90</sup> Similar lesions are common in industry Munkwitz<sup>91</sup> reports a number of cases of contact dermatitis which occurred in a lacqueing plant

Chemical structure often determines the incidence of dermatitis, for Sulzberger and Baer<sup>92</sup> find that alkali-labile compounds which combine with organic bases can sensitize the skin of guinea pigs easily On the other hand, other compounds which are alkali resistant are not so dangerous The results of patch tests in general are presented in an extensive statistical study by Rostenberg and Sulzberger<sup>93</sup>

*Fungous Infections*—Fungous infections of the skin present difficulties in the way of diagnosis Lewis, Sulzberger and Wise<sup>94</sup> describe results of cutaneous tests with various preparations of trichophytin Systemic treatment with these extracts still leaves much to be desired Lewis and Hopper<sup>95</sup> found that normal children with normal scalps rarely reacted but that some of the children with ringworm showed positive responses to the intracutaneous tests

*Poison Ivy*—Caulfield<sup>96</sup> claims that if an extract of *Rhus toxicodendron* is made with ether, the results of treatment with it are much better than if the leaves are extracted with alcohol Each of 23 patients was given from eight to twenty-six doses, after treatment the symptoms were invariably improved, and the size of the response to a patch test

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90 Rudolph, J A, and Deutsch, M Pollen Dermatitis Report of a Case, *J Allergy* 9 187, 1938

91 Munkwitz, G Hauterkrankungen in einer Lackiererei und ihre Untersuchung unter besonderer Berücksichtigung der "Lappchenprobe," *Aich f Gewerbepath u Gewerbehyg* 8 83, 1937

92 Sulzberger, M B, and Baer, R L Sensitization to Simple Compounds III Relationship Between Chemical Structure and Properties, and Sensitizing Capacities in the Production of Eczematous Sensitivity in Man, *J Invest Dermat* 1 45, 1938

93 Rostenberg, A, Jr, and Sulzberger, M B Some Results of Patch Tests A Compilation and Discussion of Cutaneous Reactions to About Five Hundred Different Substances, as Elicited by over Ten Thousand Tests in Approximately One Thousand Patients, *Arch Dermat & Syph* 35 433 (March) 1937

94 Lewis, G M, Sulzberger, M B, and Wise, F Trichophytin and Allergy to Trichophytin Observations on the Variability of Cutaneous Responses to Trichophytin, *Arch Dermat & Syph* 36 548 (Sept) 1937

95 Lewis, G M, and Hopper, M E Ringworm of the Scalp Comparative Reactions to Cutaneous Tests with Trichophytin in Children With and Without Ringworm of the Scalp, Evaluation of Therapy with Stock Vaccines in Types of Infection Resistant to Treatment, *Arch Dermat & Syph* 36 821 (Oct) 1937

96 Caulfield, A H W The Specific Diagnosis and Treatment of Poison Ivy (*Rhus Toxicodendron* Dermatitis), *J Allergy* 9 535 1938

was reduced in all. On the other hand, Bachmann,<sup>97</sup> using his purified extract in almond oil, treated 14 children, but with no success. Ginsberg and his associates<sup>98</sup> treated guinea pigs with prophylactic injections of an almond oil extract before attempting to sensitize them to poison ivy and found that the preliminary doses had no effect. Biederman<sup>99</sup> reports that *Rhus toxicodendron* (poison ivy) is closely related to *Rhus vernix* (poison oak), the latter deriving its name from the shape of the leaf, which resembles that of the oak leaf. The preparation he used was an absolute alcohol extract of the desiccated leaf. His patients gave positive reactions to patch tests with extracts of both varieties, and treatment with one seemed to be successful against the other.

#### URTICARIA

Why are cutaneous tests in urticaria so unsatisfactory? Waldbott<sup>100</sup> could find positive reactions in only 27 per cent of 168 cases, and our own experience agrees closely with his. If one looks back to serum disease, one should recall that in this condition the development of antibodies and of a positive immediate cutaneous reaction first occurs not during the active process but after lesions have cleared and the disease is over. Similarly, in pneumonia the cutaneous reaction to the carbohydrate does not appear until the fever is subsiding. It would be interesting to follow a group of patients after subsidence of attacks of urticaria and make tests when they are well. Possibly one could show that foods often play a part. On the other hand, there is ample reason to think that urticaria may depend on infections. Hansen-Pruss<sup>101</sup> was able to culture a hemolytic streptococcus from specimens of material from the throat, sputum or duodenal content in 16 cases, and when he treated the patients later with sulfanilamide the organism disappeared and the urticaria subsided. Waldbott<sup>102</sup> recognized epidermophytosis as a cause of urticaria in a patient who was also subject to hay fever.

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97 Bachmann, L. C. Prophylaxis of Poison Ivy. Use of an Almond Oil Extract in Children, *J. Pediat* **12** 31, 1938.

98 Ginsberg, J. E., Becker, F. T., and Becker, S. W. Sensitization of Guinea-Pigs to Poison Ivy, *Arch. Dermat. & Syph* **36** 1165 (Dec.) 1937.

99 Biederman, J. B. Observations on the Relation of Poison Ivy and Poison Oak, *New England J. Med* **219** 117, 1938.

100 Waldbott, G. L., and Ascher, M. S. Urticaria of the Serum Sickness Type, *J. Allergy* **9** 584, 1938.

101 Hansen-Pruss, O. C. Urticaria of Bacterial Origin, *J. Allergy* **9** 577, 1938.

102 Waldbott, G. L., and Ascher, M. S. Chronic Urticaria Recurring Every Six Weeks, Due to a Fungous Infection, *Arch. Dermat. & Syph* **36** 314 (Aug.) 1937.

## OTHER MANIFESTATIONS

The case of a boy who showed a classic Arthus phenomenon after excessive treatment with horse serum was described in the foregoing section on serum disease. Brown and his associates<sup>103</sup> describe the case of another boy, who was bitten repeatedly by mosquitoes and exhibited a series of severe local reactions, with marked inflammation going on to necrosis and scarring.

Henoch's purpura and abdominal allergy comprise a subject of practical importance because occasionally a case occurs which is mistaken for a case of appendicitis. Althausen and his associates<sup>104</sup> describe 8 cases, with emphasis on the fact that in 4 there were the typical criteria of allergy—a family history of the condition, other allergic manifestations, eosinophilia and positive reactions to cutaneous tests. The authors do well to quote Dr. J. H. Pratt, as follows: "No one should operate on a child with abdominal colic until the diagnosis of Schonlein-Henoch's disease has been excluded." The subject will be mentioned again in the section on drug allergy.

Fries and Zizmor<sup>105</sup> made roentgenographic studies of 11 children with food allergy, mixing the barium sulfate with the suspected food, but they found the peristaltic disturbances variable. Action of the stomach and bowels was increased in some cases and decreased in others, yet all the patients complained of their abdominal symptoms during the test.

## DRUG ALLERGY

Drug allergy is being recognized more and more. In many cases, like those of asthmatic patients who are sensitive to acetylsalicylic acid or to morphine, severe symptoms may develop with extraordinary speed and may lead promptly to collapse. In other cases a symptom like urticaria or purpura comes on more slowly, to produce a condition which is distressing but hardly dangerous. Between these extremes are all variations. The relation between this violent reaction to drugs and clinical allergy is not always clear. One thinks first of a toxic effect, but in most of the instances it is well recognized that the drug has been given to many persons without causing symptoms or, should one say

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103 Brown, A., Griffiths, T. H. D., Erwin, S., and Dyrenforth, L. Y. Arthus's Phenomenon from Mosquito Bites. Report of a Case with Experimental Studies, *South M J* **31** 590, 1938.

104 Althausen, T. L., Deamer, W. C., and Kerr, W. J. The False "Acute Abdomen." II. Henoch's Purpura and Abdominal Allergy, *Ann Surg* **106** 242, 1937.

105 Fries, J. H., and Zizmor, J. Roentgen Studies of Children with Alimentary Disturbances Due to Food Allergy, *Am J Dis Child* **54** 1239 (Dec) 1937.

without causing obvious symptoms and that the so-called toxicity may be a comparative and not an absolute factor

Two other factors which suggest that the reaction is allergic are, however, present in many of the cases. First, several of the patients admit that they are subject to other allergic manifestations, they have or have had hay fever or asthma or eczema, or they come of an allergic family. They may have both a personal and a family history of allergy. It is reasonable to consider that their sensitiveness to the drug is analogous to their sensitiveness to other foreign substances. Second, it is often reported that the same drug had been taken previously and apparently had not produced symptoms at that first treatment, then came an interval during which the drug was not taken. The case for actual sensitization resulting from the first course of doses can be supported with propriety.

*Drug Allergy Summary of Reports in the Recent Literature*

Author	Symptoms Produced	Causative Agent	No of Cases	Comment
Lieberherr	Thrombopenic purpura	Sedormid (allyliso propylacetylcarbamide)	2	
Hill	Thrombopenic purpura	Sedormid	2	
Kadin	Aplastic anemia	Neoarsphenamine	3	Review of literature
McCastor and McCastor	Circulatory collapse	Sodium morrhuate	2	Recovery in both cases
Sugg	Dermatitis	Cinchophen	6	Review of literature
Pfeiffer	Edema around eyes	Pontocaine, 0.5% solution	1	
Beecher	Collapse	Avertin with amylene hydrate	7	Death in all cases

The current literature includes several reports of cases of drug allergy, and a few<sup>106</sup> are selected for the accompanying table.

Insulin hypersensitivity is discussed in a thoughtful paper by Cohen and Simon,<sup>107</sup> who add their own experiences to the reports in the litera-

106 Lieberherr, W. Zur Kenntnis der 'Purpura thrombocytopenica beim Gebrauch von Sedormid, *Med Klin* **33** 475, 1937. Hill, D. B. Thrombopenic Purpura Following Allyl-Isopropyl-Acetyl-Carbamide (Sedormid), *J A M A* **111** 1459 (Oct 15) 1938. Kadin, M. Aplastic Anemia Following the Use of Neoarsphenamine, *Arch Dermat & Syph* **37** 787 (May) 1938. McCastor, J. T. N., and McCastor, M. C. Reaction to Sodium Morrhuate Injections for Varicose Veins and Hydrocele, *J A M A* **109** 1799 (Nov 27) 1937. Sugg, E. S. Acquired Sensitivity to Cinchophen. Report of Six Cases and a Review of the Literature, *Am J M Sc* **195** 473, 1938. Pfeiffer, R. L. Hypersensitivity to Pontocaine. Report of a Case, *Arch Ophth* **18** 62 (July) 1937. Beecher, H. K. Fatal Toxic Reactions Associated with Tribromethanol Anesthesia, *J A M A* **111** 122 (July 9) 1938.

107 Cohen, A. E., and Simon, F. A. Insulin Hypersensitivity, *J Allergy* **9** 503, 1938.

ture They call attention to the difference of opinion regarding the underlying cause Whether the active substance is the insulin protein itself, the animal from which it is derived or some substance developed in the manufacture is still an open question No doubt there is a variation among the cases which could account for the difficulties of study It is interesting that Bernstein and his associates <sup>108</sup> were able to sensitize guinea pigs with crystalline insulin

Liver extract likewise has given trouble in a few instances Cripp <sup>109</sup> reviews the 7 cases reported in the literature and describes a patient who had asthma and urticaria after subcutaneous doses of liver extract but who could take the drug by mouth without difficulty

In his clinical lecture at the meeting of the American Medical Association in San Francisco, T Fitz-Hugh Jr <sup>110</sup> gave an interesting and helpful review of the whole subject of drug allergy and included many useful references The history of drug allergy and the interrelation of the several manifestations were brought out clearly The paper is good Rhoads and his associates <sup>111</sup> have thrown a new light on the nature of drug sensitiveness in animals When dogs were given a diet deficient in riboflavin (vitamin B<sub>2</sub>, or G)—the so-called Goldberger diet which produces pellagra—and then were treated with drugs like aminopyrine, severe anemia developed Control animals, however, treated either with the drug alone or with the diet alone gave no such symptoms Evidently the combination of diet and drug together is important Perhaps further studies will show that drug allergy and possibly other types of allergy as well will depend on diet The thought is intriguing

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108 Bernstein, C, Jr, Kirsner, J B, and Turner, W J Studies on Anaphylaxis with Insulin, *J Lab & Clin Med* **23** 938, 1938

109 Cripp, L H Allergy to Liver Extract, *J A M A* **110** 506 (Feb 12) 1938

110 Fitz-Hugh, T, Jr Sensitivity Reactions of the Blood and Bone Marrow to Certain Drugs, *J A M A* **111** 1643 (Oct 29) 1938

111 Rhoads, C P, Barker, W H, and Miller, D K The Increased Susceptibility to Hemolysis by Indol in Dogs Fed Deficient Diets, *J Exper Med* **67** 299, 1938

## News and Comment

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**The Ella Sachs Plotz Foundation for the Advancement of Scientific Investigation**—Thirty-two grants were made by the Ella Sachs Plotz Foundation for the Advancement of Scientific Investigation during 1938. One of these was a continued annual grant, sixteen of the new grants were made to scientists outside the United States.

In the fifteen years of its existence the Foundation has made three hundred and forty grants, which have been distributed to investigators working in Argentina, Austria, Belgium, Brazil, Canada, Chile, China, Czechoslovakia, Denmark, Estonia, Finland, France, Germany, Great Britain, Greece, Hungary, Iraq (Asia), Italy, Latvia, Lebanon (Asia), Netherlands, North Africa, Norway, Palestine, Poland, Portugal, Rumania, South Africa, Sweden, Switzerland, Syria, Venezuela, Yugoslavia and the United States.

During the present great need for funds, grants will be given in the sciences closely related to medicine without reference to special fields. The maximum size of grants will usually be less than \$500.

Applications for grants to be held during the year 1939-1940 must be in the hands of the executive committee before April 1939. There are no formal application blanks, but a letter asking for aid must contain a definite statement of the qualifications of the investigator, an accurate description of the proposed research and a statement as to the size of the grant requested and the specific use of the money to be expended. Only applications complying with these conditions will be considered. It is highly desirable to include letters of recommendation from the directors of laboratories or clinics in which the work is to be done.

Applications should be sent to Dr. Joseph C. Aub, Collis P. Huntington Memorial Hospital, 695 Huntington Ave., Boston.

**Postgraduate Institute**—The fourth annual Postgraduate Institute, which will be held in the Bellevue-Stratford Hotel, Philadelphia, March 13 to 17, 1939, will be sponsored by the Philadelphia County Medical Society. Blood dyscrasias and metabolic disorders will be discussed. These subjects will be subdivided into eighty-six clinical lectures, with open forum discussion of each topic. Dr. Rufus S. Reeves, 136 South Sixteenth Street, Philadelphia, is the director of the Postgraduate Institute.



## Book Reviews

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Course of Changes in the Spinal Fluid of Syphilitics A Clinical and Catamnestic Study By Esbern Lomholt Pp 168, with 96 illustrations Copenhagen Levin & Munksgaard, 1936

This monograph, a translation from the Danish, constitutes a unique and important contribution to syphilology Lomholt has utilized the extensive clinical and serologic material of the University Clinic of Dermatology of the Rigshospital, Copenhagen, and the State Serum Institute of Denmark Thanks to the intelligent thoroughness of the Danish attack on syphilis, it was possible to follow large numbers of patients over long periods and to derive statistical information regarding changes in the spinal fluid in syphilis which is probably not available elsewhere in the medical literature

The findings are of value in understanding the development and course of neurosyphilis and lead to certain conclusions regarding treatment The book is divided into two parts The first, comprising one hundred and sixty-eight pages, deals with the changes in the spinal fluid during the three stages of syphilis and in latency, with catamnestic studies of the course of these changes The total material employed consisted of the records of 2,399 patients on whom 2,704 spinal punctures were performed during various stages of the disease The second part contains detailed tables and case records on which the studies were based Lomholt has analyzed this material with meticulous care and has considered only those statistical results in which the deviations exceeded three times the mean error

It is impossible to record in the present review more than a few of the conclusions reached in this work They are all of great interest to the physician treating patients with syphilis and emphasize many facts of value which are all too poorly known by members of the medical profession at large today

Considerable attention is given to the ancient criticism that early treatment with arsphenamine promotes the development of neurosyphilis Some of Lomholt's figures seem at first sight to support this idea Of 204 patients with untreated primary syphilis, 9 (4.5 per cent) showed slight pleocytosis, while of 121 patients with arsphenamine-treated primary syphilis, 15 (12 per cent) exhibited a similar slight pleocytosis In Lomholt's opinion, however, this apparent tendency of arsphenamine to increase the incidence of pleocytosis is more probably due to the fact that the infection is a week or two older in treated than it is in untreated patients Similar studies on treated and untreated patients during the secondary stage showed no such increase of pleocytosis in the treated patients

From a study of 693 cases of untreated secondary syphilis it was determined that the older the infection, the more frequently pleocytosis was noted While in untreated primary syphilis, pleocytosis was noted in only 4.5 per cent of the cases, the cell count was increased in 23.5 per cent of the 693 cases of untreated secondary syphilis It was found, however, that the presence of leukoderma in the secondary stage of untreated syphilis increased the percentage of cases of pleocytosis to 39, while the percentage rose to 60 in cases of secondary syphilis with iritis

Lomholt uses three criteria for "positivity" of the spinal fluid, viz, pleocytosis (more than 4 cells per cubic millimeter), an increased globulin content and a positive reaction to the Wassermann test The spinal fluids are classified as being "completely positive" (abnormal in all three respects), "combined positive" (abnormal in two of the three tests) and "isolated positive" (abnormal in only one of the three) The most frequent change in the spinal fluid in primary and secondary syphilis is pleocytosis (4.5 per cent of the cases of untreated primary and 23.5 per cent of the cases of untreated secondary syphilis), the next most

frequent change is an increased globulin content (59 per cent of the cases of untreated primary and 10.1 per cent of the cases of untreated secondary syphilis) and the least frequent change is the positive reaction to the Wassermann test (34.5 per cent of the cases of untreated primary and 3 per cent of the cases of untreated secondary syphilis)

Other interesting statistical facts brought out in the study are

1 Repeated examinations of the spinal fluid during the first series of treatments in many instances revealed rapid improvement, but in some cases pathologic changes appeared in previously normal fluid, despite treatment with arsphenamine. There were never more than "isolated positive" findings, however.

2 There was some degree of "positivity" of the spinal fluid in over 20 per cent of the cases of tertiary syphilis.

3 In 48 (16.4 per cent) of 293 cases of seronegative latent syphilis, there was some degree of "positivity" of the spinal fluid. This number included 1 "completely positive," 2 "combined positive" and 45 "isolated positive" spinal fluids. In 127 (32 per cent) of 398 cases of seropositive latent syphilis, there was some degree of "positivity" of the spinal fluid. This number included 26 "completely positive," 40 "combined" and 71 "isolated" spinal fluids. Thus the changes in the spinal fluid were much more frequent and pronounced in seropositive than in seronegative latent syphilis but were not entirely absent in the latter. There was a considerably greater tendency among men than among women for the spinal fluid to show some degree of "positivity" in seronegative latent syphilis.

Lomholt gives an interesting account of the Danish system of registration of syphilitic patients. In operation the system is highly efficient, though no file of names is employed. The patients can be identified only by tracing their numbers back to the private records of hospitals, clinics or physicians. With this system it was possible to trace more than 98 per cent of any large group of patients and to follow the course of the disease over many years. A great many interesting and important facts were discovered by Lomholt by the use of these records. Thus, of every thousand syphilitic patients, from 2 to 4 showed dementia paralytica yearly. Again, pathologic changes ascertained in the spinal fluid during latency were already demonstrable during the primary-secondary period, provided enough spinal punctures were made at the time. On the other hand, changes in the spinal fluid during the primary-secondary stage tended to subside with this period of the disease in a great many cases. It is thus not possible to predict from examinations of the spinal fluid during the early stages of syphilis which patients are eventually destined to be afflicted with neurosyphilis. Furthermore, the reaction of the spinal fluid appears never to become positive after it has proved repeatedly to be negative during latency and in the absence of any clinical relapse. Other highly interesting statistical facts are demonstrated. For instance, more than half the new male syphilitic patients were infected before their twenty-fifth year, dementia paralytica makes its appearance preferably in patients who have had one or more secondary eruptions and seldom in patients who have never had a secondary eruption. Dementia paralytica develops most frequently above fifteen to twenty years after the original infection but may occur as early as five years and not infrequently as late as thirty to fifty years after the appearance of the chancre.

Incidentally, one learns that the incidence of syphilis in Denmark dropped from 54 per ten thousand in 1919 to 3 per ten thousand in 1933. This gratifying reduction can be attributed only to the almost universal registration and intensive treatment of syphilis in Denmark. The lessons for Americans are clear. Syphilis must be attacked nationally and intensively to be controlled, treatment must be early and vigorous and no case of syphilis can be handled properly without examination of the spinal fluid. What was relatively easy in so small a country as Denmark will be much more complex and difficult in the United States, but this is the goal to be achieved.

**The Rheumatic Diseases** By Sir Leonard Hill, M D, LL D, F R S, and Philip Ellman, M D, M R C P Price, 10s 6d Pp 282 London Edward Arnold & Co, 1938

Hill and Ellman present twenty chapters based on a series of lectures delivered by fifteen authorities on the study and treatment of arthritis. These lectures were given during the winter and spring of the year 1936 to 1937 as a postgraduate course. This book has brought together good, concise presentation of what the authors thought about their respective subjects.

The social and economic aspects are reviewed, with short comments on the way the members of the medical profession and government officials in several countries are organized to treat patients with arthritis. A well presented discussion of the classifications and clinical types of arthritis helps to orient the reader. The chapters on acute rheumatic diseases of childhood and on rheumatism of the spine are particularly well presented. They are rather opinionated but contain practical and helpful suggestions. The report of the relation of antistreptolysins to chronic rheumatic diseases includes some interesting investigative work that the author has done, especially in regard to the use of sulfanilamide and some of its derivatives. The use of drugs in the treatment of the rheumatic diseases is discussed, however, little comment is made concerning their relative values. There is an excellent chapter on the orthopedic and surgical treatment of rheumatoid arthritis.

In the series of chapters on physical therapy in the treatment of arthritis there are presented good explanations of the types of physical therapy to be used and the reasons for using them. The chapter on the physical basis of these types of therapy is helpful as an introduction to the chapters that follow. The use of hydrotherapy in the treatment of rheumatic diseases is particularly well discussed. The chapters on physical action, methods used in physical therapy, indications for light therapy and the technic of local and general ultraviolet irradiation are instructive and helpful, but the claims of value seem to have been more enthusiastically presented than those of other workers in the same field.

The chapters on etiology, pathology and roentgenology contain the authors' own opinions regarding these subjects. In the chapter on roentgenology especially, many of the newer interpretations of the findings are presented, some of which have been accepted by other authorities in the field and some of which are subject to debate. The chapter on the nose and throat in relation to rheumatic diseases and the two chapters on pelvic sepsis and chronic rheumatic diseases overstress the importance of these foci and are presented with too much optimism as to the results obtained. Sciatica and brachial neuralgia are presented with tables to help in making a differential diagnosis. In the chapter on nonarticular rheumatism the authors' own views regarding causes and treatment are presented. Because there is much difference of opinion regarding these points, their views are well worth studying, but, like the others, they are not generally well accepted.

The merits of this book are the concise presentation of the opinions of fifteen physicians who are making a study of rheumatic diseases and the completeness with which chronic rheumatic diseases are discussed. It is a collection of good articles on various phases of arthritis. For the student of arthritis it should be a helpful book for reference. For the practitioner it should create a much better understanding of the problems involved in the study of the rheumatic diseases.

A fair criticism is that many points are stressed with apparently equal force, and because of this the physician is advised of so many important things to do that both he and his patient are lost in the confusion regarding where to start and where to finish. This is typical of the contemporary literature on rheumatism and should not detract too much from the value of this collection of papers.

**The Biology of Arteriosclerosis** By M C Winternitz, M D, R M Thomas, M D, and P M LeCompte, M D From the Department of Pathology, Yale University School of Medicine Price, \$4 Pp 142, with 116 illustrations Springfield, Ill Charles C Thomas, Publisher, 1938

This is a stimulating monograph, which should be of interest to students, teachers and practitioners It is written in scholarly fashion and is well printed with good illustrations As the title suggests, it deals with the pathology of vascular disease

There are nine chapters in the book, not including an introduction, a foreword, a concluding chapter and two bibliographies The first of the bibliographies was assembled by the authors and is referred to throughout the text, the second was first published by Dr Elizabeth Ramsey in her review of the literature on nutrition of the blood vessels in the *Yale Journal of Biology and Medicine*, in October 1936, and now has been brought up to date These two bibliographies are comprehensive

The foreword gives a pleasant account of the background which led the authors to undertake the studies described in the body of the volume, and the introduction tells the reader what these studies are "The material presented deals primarily with the interpretation of the morphology of arteriosclerosis, with emphasis upon the vascularity of the vessel wall and its relation to the disease manifestations of the intima Evidence is offered for the interpretation of the inception of the processes as well as for the various sequences that follow in its wake A unifying concept which embraces many different manifestations of disease in the cardiovascular system including the arteries, veins, and heart valves is evolved"

The authors then proceed to present their point of view on vascular disease clearly and in an interesting manner Their final conclusion is plainly understandable—the problem of arteriosclerosis may be approached by logically considering the artery as an organ subject to the same pathologic changes as are other tissues, instead of by regarding most vascular lesions as of degenerative origin and the inevitable concomitant of age

**The Biology of Pneumococcus** By Benjamin White, Ph D, with the collaboration of Elliott Stirling Robinson, M D, Ph D, and Laverne Almon Barnes, Ph D Price, \$4.50 Pp 820, with illustrations New York The Commonwealth Fund, 1938

This book represents a review of the literature on the biology of the pneumococcus resulting from the studies on pneumonia carried out by the Massachusetts Department of Public Health during the years 1931 to 1935 under a grant from the Commonwealth Fund It comprises a sorting out and evaluation of the literature of the past fifty years The first chapter is appropriately historical and in the sixteen subsequent chapters is followed by a detailed and orderly analysis of the present knowledge of the pneumococcus Discussion of morphology, cultural methods and peculiarities, biochemical features, classification, dissociation and related phenomena, pathogenicity for animals and man, chemical constituents, polysaccharide-splitting enzymes, antigenicity and antibodies, immunity, vaccines, chemotherapy and serum treatment lead to a final chapter on unsolved problems An appendix on special methods includes facts relating to mediums, isolation of the pneumococcus, type determination, preparation of polysaccharides and bacterial enzymes, serologic reactions, potency and sterility tests on antipneumococcus serum and the preparation of diagnostic rabbit serum

Each chapter is briefly summarized after the more complete exposition of the phase of pneumococcal activity under discussion In this way a correlation of the 1,593 cited references is obtained

This sorting of all the literature on the bacteriologic, biochemical and immunologic characteristics of the pneumococcus, with emphasis on the most important events in the development of knowledge in this field, represents a tremendous task

which will be of invaluable aid not only to those working in the research aspects of pneumococcic disease but also to those whose casual interest demands at times ready reference to any phase of pneumococcic infection. The purpose behind this text could well be applied to many other fields of medical knowledge.

**Bile Its Toxicity and Relation to Disease** By O H Horrall Price, \$4  
Pp 434 Chicago University of Chicago Press, 1938

A bibliography of no less than 2,177 titles gives an idea of the scope of this compendium, which is surely an unsurpassed reference book on the subject of the bile. Unfortunately the text is made up of terse and often disjointed statements of fact or experimental work, there is no smooth continuity or unified point of view. Indeed the reviewer found it practically impossible to plough straight through this plexus of more or less uncoordinated statements. It was a surprise also not to find chemical formulas for bile pigments and acids given anywhere in the text. None the less, as an encyclopedia on bile, the book should prove most useful.

**Subacute and Chronic Pericardial and Myocardial Lesions Due to Non-Penetrating Traumatic Injuries** By Erik Warburg Translated by Hans Andersen and Gerda Seidelin Price, 12 s 6 p Pp 147, with 17 illustrations  
London Humphrey Milford, 1938

The question of damage to the heart as a result of an extreme nonpenetrating injury is not only of interest but of great practical importance. Especially in medicolegal cases does this problem come up. The present scholarly study should be especially valuable to physicians since all the literature on the subject, with detailed case reports, is assembled. Many of the cases are not entirely clear, since autopsies were not always done, but the author has assembled the best information available. It seems clear that severe damage to the heart and pericardium may often result from external trauma.

**Clinical Chemistry in Practical Medicine** By C P Stewart and D M Dunlop Second edition Price \$4 Pp 372, with 38 illustrations  
Baltimore William Wood & Company, 1937

This little book deals with the "chemical" diagnostic procedures commonly used in the clinic. In addition to descriptions of technic, there are brief paragraphs on the rationale of the various tests. Some of the outstanding topics are basal metabolism, acid base balance and renal function. The main criticism of this work is that little seems to be added to what is already readily accessible in a dozen places. The section on examination of the stomach contents displays a disregard of modern concepts and is the most unsatisfactory part of a book which at best arouses little enthusiasm.

**A B C of the Vitamins A Survey in Charts** By Jennie Gregory, M S  
Foreword by Walter H Eddy, Professor of Physiological Chemistry,  
Teacher's College, Columbia University Price, \$3 Pp 93, with 56 charts  
Baltimore Williams & Wilkins Company, 1938

This book presents the known facts relative to the distribution and the function of the vitamins in a graphic fashion that is reminiscent of one's early school days. It presents no new material but does cover a rather wide field with a reasonable degree of accuracy. The subject matter is presented entirely in charts that are carefully prepared and well done. It provides the reader with an easy and pleasant method of becoming acquainted with the subject and provides the lecturer with some ready-made charts that will aid in introducing the subject to his audience.

## ETIOLOGY OF ULCERATIVE COLITIS

### I THE PREPARATION, CARE AND SECRETIONS OF COLONIC EXPLANTS IN DOGS

ROLF LIUM, M D

AND

JOSEPH PORTER, M D

BOSTON

In an endeavor to investigate the cause of ulcerative colitis, colonic explants were chosen as the most suitable preparation for study of the reactions of the colon under direct vision. The method of preparing such explants was first described by Drury, Florey and Florey<sup>1</sup>. These investigators included no detailed account of the care given the explants except to say that dressings were applied. They reported that the surface of the explants was redder than that of the normal colon because of contact with the air and with the dressings. Raiford and Eberhard<sup>2</sup> used a similar preparation, but without protective dressings<sup>3</sup> and reported changes in the surface structures of the explants resembling those due to chronic inflammation. It is our purpose in the present paper to show that with careful attention the explant can be maintained indefinitely in what appears to be a normal condition so far as its gross as well as its microscopic appearance is concerned. As a part of this study, quantitative measurements of the secretion of the explants were made.

### METHODS

Fifteen medium-sized dogs were used in these and subsequent experiments<sup>4</sup>. With the animal under pentobarbital sodium anesthesia (intravenous), a section approximately 3 cm. in length was resected from the midportion of the colon.

From the Surgical Research Laboratory, the Fifth Surgical Service (Harvard), and the Mallory Institute of Pathology, of the Boston City Hospital.

1 Drury, A. N., Florey, H., and Florey, M. E. The Vascular Reactions of the Colonic Mucosa of the Dog to Fright, *J. Physiol.* **68** 173, 1929.

2 Raiford, T. S., and Eberhard, T. Pathological Changes in Exteriorized Gastro-Intestinal Grafts, *Ann. Surg.* **104** 175, 1936.

3 Raiford, T. S., and Eberhard, T. Personal communication to the authors.

4 Lium, R. Etiology of Ulcerative Colitis. II. Effect of Induced Muscular Spasm on Colonic Explants in Dogs, with Comment on Relation of Muscular Spasm to Ulcerative Colitis. *Arch. Int. Med.*, this issue, p. 210.

An end to end anastomosis was done by the Parker-Kerr technic. The resected segment was then brought outside with the mesenteric pedicle intact. The layers of the abdominal wall were sutured loosely around this pedicle, and a section of skin, the size and the shape of the graft, was then excised. The segment of colon was opened along its antimesenteric border and sewed to the edges of the area of excised skin. The edges of the explants were usually firmly healed and adherent to the cutaneous incision at the end of ten days. Figure 1 shows the appearance of the preparation in dog 4 after healing was complete.

For 7 animals (dogs 1 to 7) a quantitative study was made of the secretion of mucus by the normal graft according to the following technic. Clean dressings were dried in an oven at 45 C for twenty-four hours and accurately weighed. They were immediately applied to the graft and twenty-four hours later were removed and weighed at once. The dressings, with the adherent secretion, were dried again at 45 C for twenty-four hours and again weighed. The figures gave the amount of solid plus moisture secreted by the graft and the amount of total



Fig 1—The appearance of a graft twenty days after preparation. The photograph also shows the adhesive binder used to hold the dressings in place.

dry solids, respectively. The error due to evaporation was reduced to a minimum by the use of absorbent dressings which were covered by a heavy adhesive binder of double thickness.

With this method the daily amount of mucus secreted was determined during control periods of normal feeding. The effect of changes in the character of the stools was noted during such periods, and subsequently the effect of starvation and of dehydration due to vomiting and diarrhea was observed. The effect on the amount of secretion of leaving the dressings in place for two days instead of changing them daily was determined. Finally the progressive changes in the explant were observed when the dressings were left off for one month.

## RESULTS

Severe spasm was present in the musculature of the graft during the twenty-four hours immediately after its preparation. It was noted that ulcers appeared in the central portion of the preparation, where no

trauma had been inflicted After this initial period the muscular spasm disappeared, the ulcers healed and the grafts, which were treated by daily dressings, looked perfectly normal for long periods Figure 2 is a photomicrograph of the mucosa from a graft in dog 6 which had been prepared eight months previously In figure 3 is shown for comparison a microscopic section of normal colonic mucous membrane from dog 8 Careful study of these two preparations showed no appreciable difference

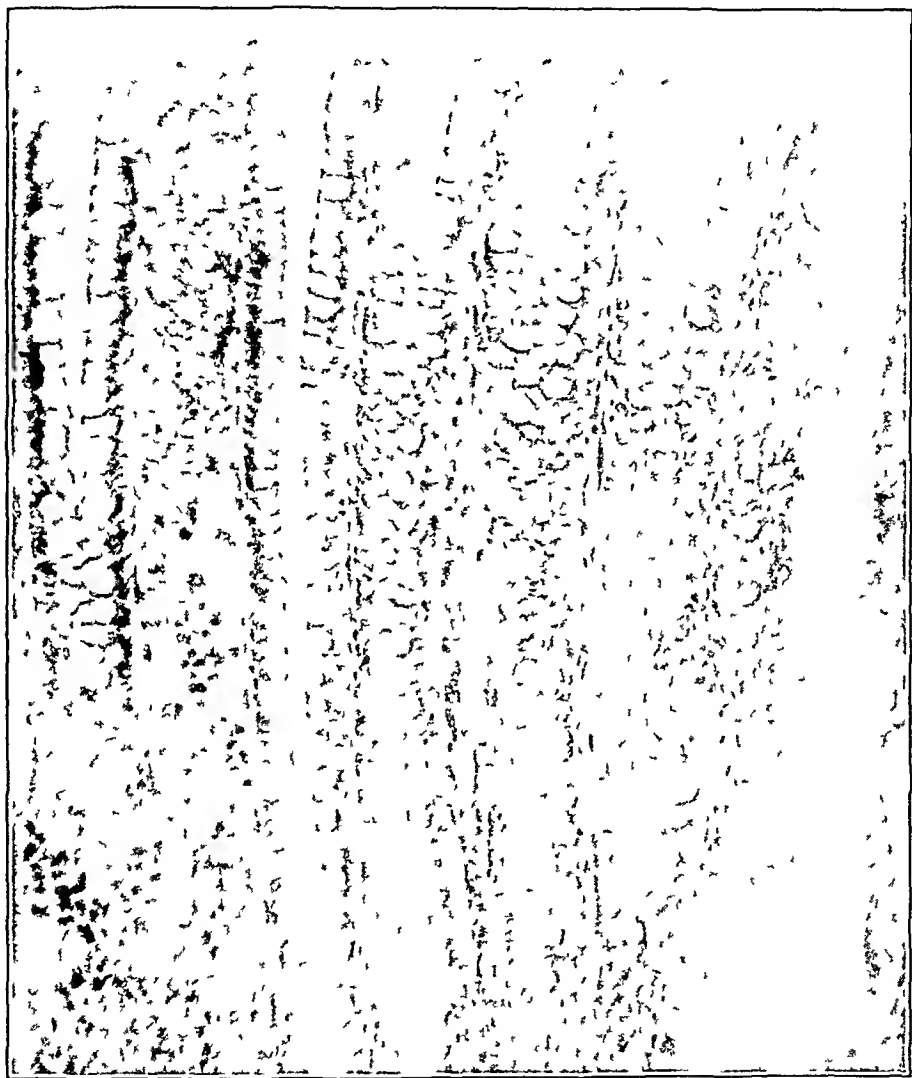


Fig 2—Photomicrograph ( $\times 200$ ) of a normal, resting graft eight months after preparation

During the period of healing, which was from ten to fourteen days on the average, there was at first a thin, watery secretion of mucus This gradually changed during the first ten days after operation to the typical thick mucus which was found in a layer on the dressing whenever the latter was removed

The application of a dressing to a normal graft invariably caused an immediate visible increase in muscular tone and a prompt secretion of



mucus In twenty-four hours a layer approximately 2 mm thick and exactly equal to the size of the graft was found There was also some moisture diffused throughout the dressing Table 1 shows the amount of mucus and solids secreted daily by dog 11 over a twelve day period of normal feeding Whether the stools were hard or soft appeared not to influence significantly the daily amount of secretion In all 7 animals similar results were found during such control periods No constant

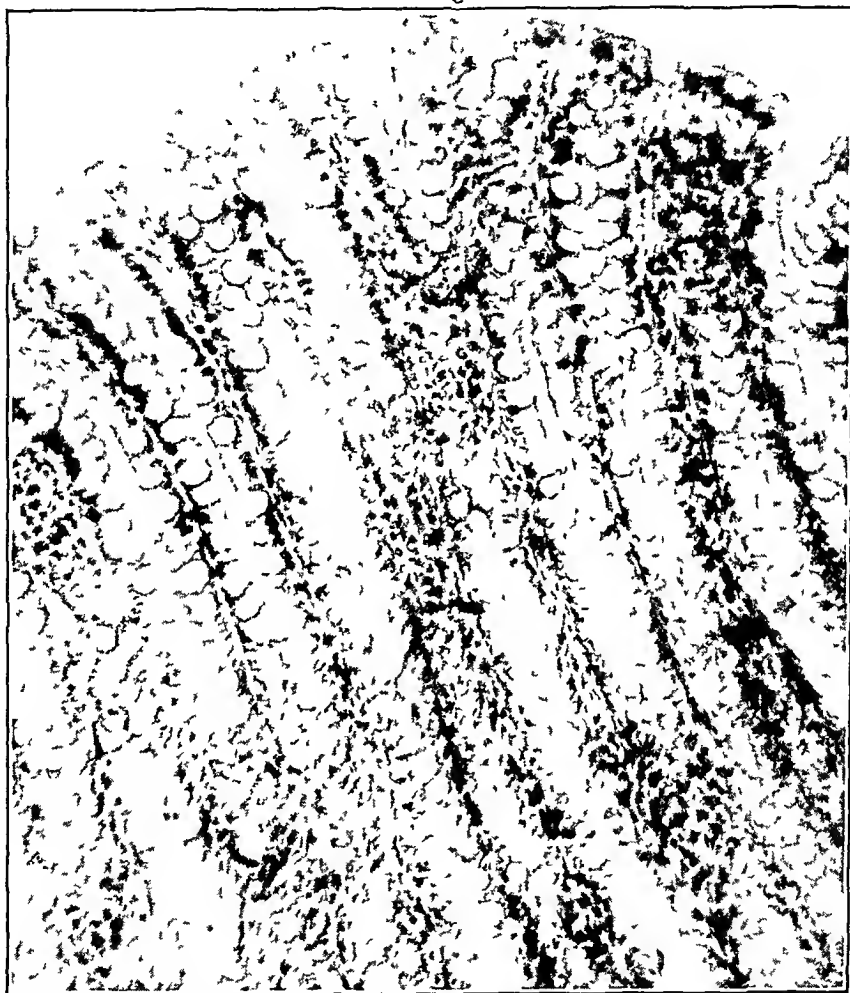


Fig 3—Section ( $\times 200$ ) of normal colon taken from a dog at death

relation could be established between the amount of secretion and the surface area of different grafts

In each of 3 other animals (dogs 7 to 9) that were starved for a period of four days, the secretion of mucus by the graft was not measurably diminished as compared with the secretion during the control period of normal feeding Table 2 shows for comparison the values for these animals during four day periods of feeding and starvation Three other animals (dogs 10, 13 and 14) evidenced no measurable change in the total amount of secretion on the dressing when it was left in place for

forty-eight hours instead of being removed every twenty-four hours, as was done during the preceding control period. The results are shown in table 3.

TABLE 1—*Daily Amount of Mucus Secreted by the Colonic Graft in Dog 11 Over a Period of Twelve Consecutive Days*

Date	Weight of Secretion, Gm		Type of Stool
	Mucus	Solids	
4/3	2.86	0.25	Formed, hard
4	2.75	0.19	Formed, soft
5	2.54	0.40	Formed, soft
6	2.09	0.30	Loose
7	4.33	0.36	Formed, hard
8	2.91	0.34	None
9	3.19	0.34	Formed, soft
10	3.08	0.29	Formed, soft
11	2.39	0.33	Formed, soft
12	3.05	0.43	Diarrhea
13	4.34	0.37	Formed, soft
14	3.76	0.32	Hard, small pieces

TABLE 2—*Daily Amount of Mucus and Solids Secreted During Alternate Four Day Periods of Starvation and Feeding*

Dog No	Diet	Date	Weight of Secretion, Gm			
			Mucus		Solids	
			Daily	Total	Daily	Total
7	Starved	5/16	3.71		0.47	
		17	3.65		0.35	
		18	3.50		0.52	
		19	2.96		0.59	
				13.82		1.93
	Meat and milk	20	2.90		0.45	
		21	3.73		0.56	
		22	3.69		0.57	
		23	3.26		0.50	
				13.58		2.08
8	Starved	5/19	2.80		0.62	
		20	3.18		0.63	
		21	3.26		0.54	
		22	2.04		0.46	
				11.28		2.25
	Meat and milk	23	2.99		0.54	
		24	2.03		0.65	
		25	1.91		0.10	
		26	2.87		0.39	
				9.80		1.68
9	Starved	5/19	2.48		0.68	
		20	3.26		0.64	
		21	2.07		0.50	
		22	1.93		0.45	
				9.74		2.27
	Meat and milk	23	2.25		0.41	
		24	1.43		0.16	
		25	1.68		0.42	
		26	1.74		0.49	
				7.10		1.48

Two of the animals (dogs 5 and 6) suffered from marked dehydration. Dog 5 had intractable vomiting and dog 6 suffered from almost continuous diarrhea. Table 4 shows the marked diminution in the weight

of the secretion on the dressings of both explants during these periods. The dry solids, which were measured only for dog 5, were diminished proportionately with the total secretion.

TABLE 3—*Weight of Mucus and Solids Secreted When Dressings Were Changed Daily Compared with Weight When Dressings Were Left in Place for Two Days*

Dog No	Date	Number of Days	Weight of Secretion, Gm	
			Mucus	Solids
10	5/24	1	2.99	0.54
	25	1	2.03	0.04
	26	1	1.91	0.10
	27	1	2.87	0.27
	29	2	2.90	0.23
13	5/22	1	3.73	0.57
	23	1	3.69	0.50
	24	1	3.26	0.50
	26	2	3.19	0.46
14	5/24	1	2.25	0.41
	25	1	1.43	0.16
	26	1	1.68	0.30
	27	1	1.74	0.31
	29	2	1.87	0.31

TABLE 4—*The Amount of Mucus Secreted During Periods of Normal Nutrition and Periods of Dehydration*

Dog No	Condition	Date	Weight of Secretion, Gm		
			Mucus	Solids	
5	Meat and milk	3/20	2 53	0 31	
		21	2 18	0 22	
		22	2 47	0 13	
		23	5 00	0 22	
		24	3 52	0 20	
	Average		3 14	0 21	
		Vomiting	3/31	1 03	0 02
			4/ 1	1 20	0 09
			2	1 28	0 06
			3	1 61	0 10
4	1 24		0 05		
Average		1 27	0 06		
	6	Meat and milk	3/ 1	4 05	
2			3 75		
3			3 90		
4			3 80		
5			3 14		
Average			3 72		
		Diarrhea	3/ 6	1 73	
			7	0 21	
			8	0 92	
			9	1 07	
10	1 50				
Average		1 08			

In order to determine why in the experiments of Raiford and Eberhard pathologic changes were noted in the explants, 2 animals (dogs 12 and 13) were allowed to go without protective dressings over the explant for a period of one month, when microscopic sections were made. Dur-

ing this period the dogs licked their grafts frequently, and shavings and sawdust from the cage would rub across the surfaces. Within one day after the dressing was abandoned these explants lost their rugae and showed flattened surfaces. Their gross appearance was distinctly that of chronic inflammation, and after three days small ulcers were noted on the surfaces. Figure 4 is a photomicrograph of a section from such

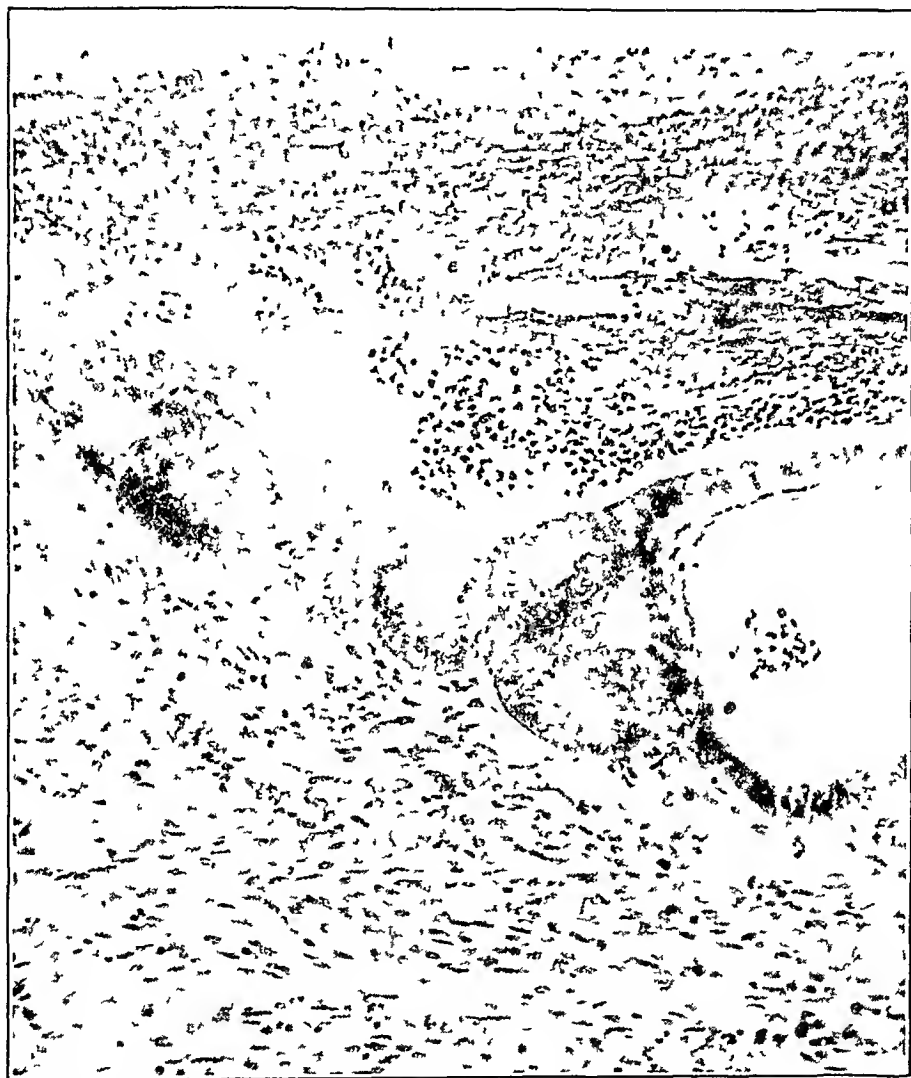


Fig 4—Photomicrograph ( $\times 200$ ) of a section of mucosa from a colonic graft exposed without a dressing for one month. Note the marked inflammatory reaction, the absence of mucus and the loss of the normal deep glands.

a preparation (dog 12) taken thirty days after the beginning of exposure. There are a marked inflammatory reaction in the submucous tissues and a layer of fibrin with inflammatory cells on the surface. This particular section was made through the edge of an ulcer which is seen in the photomicrograph. Only an occasional goblet cell can be seen. Sections taken thirty days after the beginning of exposure of the graft (animal 13) were similar.

## COMMENT

So long as colonic explants are covered with dressings they appear normal and cannot be differentiated microscopically from normal colon. These findings are in agreement with those of Druy, Florey and Florey.<sup>1</sup> Prolonged exposure of two grafts without dressings demonstrated that the similar chronic inflammatory changes noted in such explants by Rarford and Eberhard were probably due to the absence of protective dressings. None of our protected grafts showed pathologic changes, and grafts which had been uncovered for a week healed promptly on resumption of regular dressings.

The amount of mucus secreted in twenty-four hours was relatively constant for a given graft. The consistency of the amounts of this secretion during the control periods and periods of starvation suggests that the initial mechanical stimulation due to the application of the dressing is largely responsible for the amount of secretion that is formed. This is further substantiated by the finding that the amount of secretion on the dressing was the same whether the dressing was changed after twenty-four or after forty-eight hours. The conclusion of Florey<sup>5</sup> that the secretion of mucus by the explants is a response to superficial mechanical irritation is thus confirmed. Once the mechanical irritation of the dressing has been removed by the interposition of a layer of mucus between it and the graft, secretion of mucus apparently stops. The physiologic importance of the mucus in protecting the normal colon from superficial mechanical irritation is thus suggested.

That superficial irritation is the sole cause of secretion of mucus by the colon as an intact organ or is indeed the proximate cause of secretion of mucus is, however, not a necessary conclusion from the present observations, nor is this conception substantiated by the work of Larson and Borgen.<sup>6</sup> These investigators carried out extensive observations on the secretion of mucus by an isolated loop of dog colon. Because fecal material did not traverse the loop, local mechanical irritation was absent in their experiments, yet secretion of mucus was appreciably increased at the time of defecation and whenever cathartics were administered. In the present studies it was noted that whenever a fresh dressing was applied, muscular contraction, together with an outpouring of mucus, took place in the graft. No significant variations were noted in our experiments with respect to whether the stools were formed or solid. Indeed, there was remarkable constancy of secretion, regardless of whether the animal was fed or starved. It may well be that the irritation caused by the dressing was such a dominant factor in determining

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5 Florey, H. W. The Secretion of Mucus by the Colon, *Brit J Exper Path* **11** 348, 1930.

6 Larson, L. M., and Borgen, J. A. Action of Cathartics on Isolated Dog's Colon. Secretory Activity, *Arch Surg* **27** 1120 (Dec.) 1933.

the amount of secretion by the method used that increases in the amount of secretion associated with muscular activity due to the defecation reflex were overshadowed

In later experiments, reported elsewhere in detail,<sup>4</sup> it was found that the resting explant of colon secreted a thick layer of mucus whenever it was stimulated to muscular activity by various means. Mucus is thus apparently secreted whenever natural or artificially induced muscular activity takes place and is apparently expressed from the goblet cells by the action of the underlying muscles

#### CONCLUSIONS

The colonic explant in dogs prepared by the method of Diury, Florey and Florey represents normal bowel wall so long as it is continually protected with dressings

The secretion of mucus by such grafts when dressed each day is remarkably constant and is little influenced by the digestion of food or by starvation. Dehydration, on the other hand, markedly diminishes the amount of secretion

Secretion of mucus by the colonic explant appears to be largely a response to the initial mechanical stimulation of the dressing, which is associated with muscular contraction. The layer of mucus once formed on the dressing protects the graft from further stimulation

The dominant effect of irritation caused by the dressing in inducing muscular contraction and secretion of mucus probably explains our failure to observe increases in secretion brought about by normal reflex muscular activity, as noted by Larson and Barger

Dr S Maddock supplied the animals and the facilities for conducting these experiments. Dr W B Castle advised with us concerning the preparation of the manuscript. Dr C K Drinker made available the facilities for preparing the photomicrographs

# ETIOLOGY OF ULCERATIVE COLITIS

## II EFFECT OF INDUCED MUSCULAR SPASM ON COLONIC EXPLANTS IN DOGS, WITH COMMENT ON RELATION OF MUSCULAR SPASM TO ULCERATIVE COLITIS

ROLF LIUM, MD

BOSTON

In the preceding article<sup>1</sup> a method was described of preparing colonic explants in dogs and of quantitating the secretion of mucus by such explants. On the days immediately after the preparation of the explants, ulcers were found near the center of the grafts. A feature constantly associated with this phenomenon was marked muscular spasm of the explants. When dressings were continuously used the initial muscular spasm disappeared, the ulcers healed and the grafts retained indefinitely a normal gross and microscopic appearance. Thereafter, mucus was secreted largely in response to the initial mechanical stimulation of the dressings, and this secretion was associated with muscular contraction.

It was noted that chronic surface irritation produced by leaving the grafts without dressings for forty-eight hours led to muscular spasm and an initial copious outpouring of mucus. This was soon replaced by a more watery secretion, at a time when microscopic study of the mucosa showed that the goblet cells contained no mucus. The explants showed edema, ulceration and other signs of chronic inflammation. These observations suggested that it might be worth while to study further the effect of severe muscular spasm of the explant when induced by various means. It was hoped thereby to determine the factors underlying the development of pathologic states in the preparation and to discover from their sequence a possible relation to ulcerative colitis.

### EXPERIMENTS

Explants of the colon were prepared and protected, according to the method already described, in 15 dogs. These animals were given daily a routine diet of meat and milk.

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From the Surgical Research Laboratory and the Fifth Surgical Service (Harvard) of the Boston City Hospital.

1 Lium, R, and Porter, J. Etiology of Ulcerative Colitis. I. The Preparation, Care and Secretions of Colonic Explants in Dogs, Arch Int Med, this issue, p. 201.

## 1 EFFECT OF MUSCULAR CONTRACTION PRODUCED BY MECHANICAL STIMULI

Stimulation of the graft was made in separate experiments on 9 dogs by wiping with gauze, by pinching with a hemostat and by exposure without a dressing for forty-eight hours. In order to estimate the muscular activity of the explant after stimulation, the longitudinal and transverse diameters passing through the center of the explant were measured at intervals of a minute for five minutes before the experiments commenced and at frequent intervals thereafter. Once the experiment was begun, the number of measurements taken depended somewhat on the activity of the muscles. It was assumed that the transverse diameter was an indication of the function of the circular fibers and that the longitudinal diameter was an indication of the function of the longitudinal muscle fibers.

In 5 cases (dogs 1 to 5) control measurements were taken daily for two weeks. Immediately after each control period the graft was wiped with an ordinary gauze sponge from right to left in line with the circular muscle fibers. It is obviously impossible to quantitate such a stimulus accurately, hence only two grades of pressure were used—heavy and light. When the graft was stroked once lightly with gauze, only mucus came away, and the graft showed some contraction. There was no evidence of significant trauma. If a second light stroke was applied immediately after the first, a little mucus was wiped away, and the graft showed fine bleeding points on its surface. When a single heavy stroke was made over the surface of the resting graft, mucus was wiped off the surface, and the graft bled at once and contracted more forcibly and longer than when a light stimulus was used. The duration of the contractions that followed such stimulation varied in the same graft from time to time and in different grafts, but it was always true that the heavy stimulus produced a greater response than the light stimulus. The changes in the size of the graft in dog 2 that resulted from light and heavy stimulation on different days are given in table 1. After a heavy stimulus with gauze the hemorrhage from the surface was markedly increased by the severe muscular contractions that developed, and large amounts of thick mucus mixed with blood were poured onto the surface.

Three grafts (in dogs 3 to 5) were pinched with an ordinary hemostat in three places after control measurement of the graft. Only the mucosa was included in the bite of the snap, which was removed immediately after the trauma had been inflicted. This led to severe spastic contraction of such marked degree that the graft felt like a mass of cartilage. At times the graft relaxed slightly, only to resume its severe contractions. Immediately after the pinching, a large amount of mucus was poured out on the surface. Not only was there bleeding from the points damaged by the snap, but petechial hemorrhages appeared beneath the mucosal surface in the areas that had not been pinched. At times these areas bled into the mucous coat on the surface of the graft.



The contractions lasted for one-half hour and gradually ceased during the ninety minute period of observation, at the end of this time, however, the graft had not reached its original size. The graft had returned to its usual size on the day after the pinching, and in four days, dressings being applied, the traumatized areas were completely healed. The following protocol gives the data for one of these experiments.

*Dog 4—The effect of pinching the mucosa of the explant in three places with a hemostat*

2 24 The graft was in excellent condition. No evidence of surface irritation was seen. The graft measured 4.7 by 3.7 cm.

3 55 p m A Kelly clamp was applied to the mucous membrane in three places. The size of the graft immediately afterward was 4.4 by 3.3 cm.

4 03 p m The graft measured 4 by 3.7 cm.

4 05 p m The graft measured 4.2 by 3.8 cm. It was hard, and the mucous membrane was piled up into wide rugae.

TABLE 1—*The Effect on the Dimensions of the Explant (3.6 by 3.4 Cm) in Dog 2 from Light and from Heavy Stimulation with Gauze\**

	Light Stimulation		Heavy Stimulation	
	Length, Cm	Width, Cm	Length, Cm	Width, Cm
Immediately	2.7 3.0 3.3	3.4 3.5 3.5	2.5 2.5	2.5 2.9
1 minute	3.5	3.5	3.0 3.1 3.1	2.9 2.9 3.1
2 minutes	3.5	3.4	3.1 3.2 3.2 3.3	3.3 3.2 3.3 3.5
3 minutes	3.5	3.4	3.3 3.4	3.5 3.3
4 minutes	3.5	3.4	3.5 3.5	3.3 3.3
5 minutes	3.5	3.4	3.5	3.3

\* During a control period of five minutes measurements were made at one minute intervals. No change was noted.

4 11 p m The graft measured 4 by 3 cm. It had a stony hard surface. It bled freely from the surface, and there was a liberal coating of mucus.

4 20 p m The graft measured 4 by 3.5 cm. It showed petechial hemorrhages beneath the mucosa in places other than those pinched. Some of these had ruptured onto the surface. The mucosal surface appeared inflamed, it was edematous and was covered with a  $\frac{1}{8}$  inch (0.3 cm) layer of mucus.

4 30 p m The graft measured 4.3 by 3.5 cm.

5 00 p m The graft measured 4.3 by 3.5 cm. It was inflamed and showed considerable oozing from the surface of blood and thin, watery secretion. A dressing was applied.

2/25 The graft felt soft. The mucous membrane between the pinched areas appeared normal, and the damaged places were healing.

2/28 The graft was completely healed. There was no evidence of the damaged places.

In 4 animals (dogs 7, 8, 9 and 12), after suitable measurement of the control dimensions of the graft, the dressings were removed for forty-eight hours. The preparations were thus exposed to surface irritation from licking and contact with the debris in the cage. The change in the appearance and the size of the grafts and the daily secretion of mucus were all carefully studied. In one series of experiments biopsies were made of all four explants forty-eight hours after removal of the dressings. In another series of similar experiments the amount

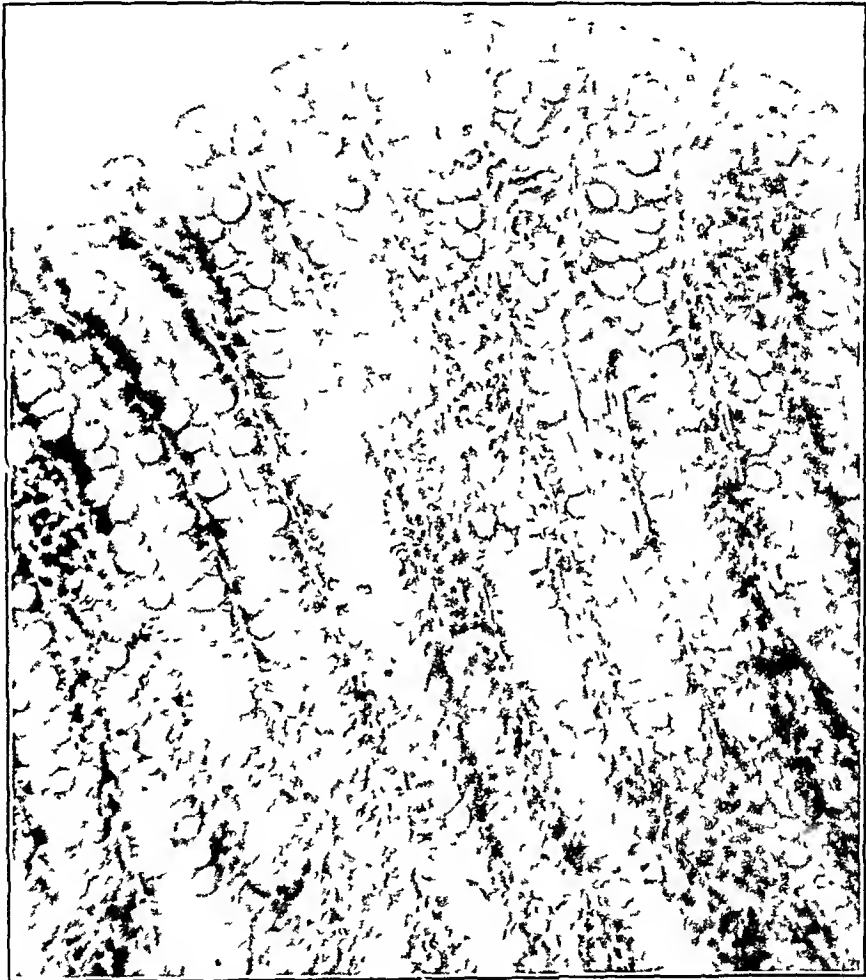


Fig 1—Photomicrograph of a normal, resting graft,  $\times 200$

of mucus secreted was weighed by the method described in the preceding article <sup>1</sup>

After exposure for forty-eight hours the graft became red and indurated and lost its normal rugae. The surface either was almost flat or was thrown into wide folds that were three times the width of normal rugae. Microscopically the grafts showed complete absence of goblet cells, fibrin appeared on the surface, loss of surface continuity was noted in certain places and evidences of inflammation were seen in the mucosa. Figure 1 is a photomicrograph of a normal colonic

explant which had been protected with dressings. Figure 2 shows an explant forty-eight hours after removal of the dressing. In all 4 animals the grafts decreased in length. In 3 the width remained essentially the same as before exposure, but in dog 12 the width increased slightly. Table 2 gives the actual measurements for this series of animals. The results were essentially the same in all 4 animals.

At the end of the forty-eight hour period of exposure, dressings were reapplied and changed daily. The layer of mucus that was



Fig. 2—Photomicrograph ( $\times 200$ ) of a graft forty-eight hours after exposure without dressings. Note the absence of goblet cells, the increased cellular reaction and the loss of surface continuity.

secreted during the first twenty-four hours after exposure was much thinner than that normally laid down. The film of mucus could scarcely be seen on the gauze, whereas normally it was a glistening layer about 2 mm thick. The dressing was saturated with moisture, indicating a serous type of secretion. The increase in the dry weight of the material secreted on the dressings was not proportionate to the increase in the liquid weight, showing that the secreted material con-

tained more water and less solids than the mucoid secretion formed by the normal graft Table 3 gives the daily amounts secreted by dog 7 in two experiments and by dog 12 in one experiment

TABLE 2—*The Effect of Exposure to Surface Irritation on the Size of the Colonic Explant*

Dog No	Average Dimensions of Explant Before Exposure, Cm		Average Dimensions of Explant After Exposure, Cm	
	Length	Width	Length	Width
7	3.8	3.6	3.1	3.5
8	5.8	4.7	5.0	4.7
9	5.4	4.4	4.4	4.1
12	4.4	3.3	3.9	3.7

TABLE 3—*Effect of Exposure Without Dressings for Forty-Eight Hours on the Subsequent Amount of Secretion by the Colonic Graft*

Dog 7 First experiment		Weight of Mucus, Gm	Weight of Solids, Gm
Control	Date		
	4/18	5.63	0.18
	4/19	5.58	0.47
	4/20	5.31	0.40
	4/21	4.76	0.55
After 2 days of exposure without dressings			
	4/24	21.13	0.24
	4/25	10.43	0.51
	4/26	5.00	0.39
	4/27	5.47	0.65
Dog 7 Second experiment			
Control	Date		
	4/28	5.57	0.22
	4/29	5.72	0.32
	4/30	4.92	0.30
	5/ 1	3.91	0.33
After 2 days of exposure without dressings			
	5/ 4	13.83	0.15
	5/ 5	15.61	0.38
	5/ 6	3.47	0.74
	5/ 7	4.75	0.32
Dog 12 First experiment			
Control	Date		
	5/ 1	6.18	0.25
	5/ 2	5.50	0.39
	5/ 3	5.80	0.54
	5/ 4	4.90	Not done
After 2 days of exposure without dressings			
	5/ 7	19.28	0.47
	5/ 8	11.71	0.35
	5/ 9	5.56	0.33
	5/10	4.34	0.32

When daily dressings were resumed, the amount of mucus of the normal, thick variety increased rapidly, and within seventy-two hours a good layer was found on the dressings, with only the usual slight amount of moisture diffused throughout. It is of interest that 2 animals

(dogs 7 and 9) scratched their grafts and so produced ulcers, which were not covered with mucus until healing had occurred. After dressings had been reapplied for one or two days, the mucosal surface of the explants appeared normal except for any ulcerations that had formed. However, all the explants which had been protected for twenty-four to forty-eight hours bled much more readily when stroked lightly with gauze than those which had been at rest and protected for several weeks. It seemed as if the regenerating epithelium were much more sensitive to trauma than that of the normal, resting explant.

## 2 EFFECT OF MUSCULAR CONTRACTION PRODUCED BY ACETYLCHOLINE AND PROSTIGMINE

From the work of Dale and Dudley<sup>2</sup> it has been established that acetylcholine is parasympatheticomimetic in its action. Prostigmine enhances this activity by inhibiting the esterase which normally hydrolyzes acetylcholine in the tissues.<sup>3</sup> In order to produce maximum muscular activity in the explant, these two agents were combined. One-half cubic centimeter of 1:4,000 solution of prostigmine was given intravenously, and immediately thereafter at five minute intervals for forty minutes 0.2 cc of a 1 per cent solution of an acetylcholine salt was applied on the surface of the graft.

In all 6 animals (dogs 9, 11 to 15) the grafts contracted violently immediately after the acetylcholine was applied and remained in a state of almost constant spastic contraction during the application of this agent. Within fifteen minutes every explant showed petechial hemorrhages, which gradually increased in size and coalesced. In the dogs which showed a maximum response, the surface at the end of an hour appeared like a piece of raw beef. There was a rich secretion of thick mucus during the early part of the experiment, but this gradually changed to a thin, watery secretion. On the day after the experiment the grafts still appeared somewhat inflamed, and small flecks of blood were found in the mucous coating. After forty-eight hours the grafts again looked normal. The following protocols give the data for the experiments on dogs 14 and 15.

### Dog 14—*The results of experiments with acetylcholine and prostigmine*

6/12/37, 4:45 p. m. Prostigmine (1 cc, 1:4,000) was given intravenously. Acetylcholine chloride was placed on the surface of the graft. Every five minutes during the next forty minutes, 0.2 cc of a 1 per cent solution was applied.

4:50 p. m. A violent spasm of the graft was followed by blanching, and the graft turned pale yellow. On relaxing, it became pink, but immediately afterward a contraction of two minutes' duration set in.

4:52 p. m. The graft was beginning to appear swollen, and small petechiae were visible beneath the surface of the epithelium. There was a generous secretion of thick mucus on the surface. Alternate contraction and relaxation occurred, but the graft did not relax to its original size.

<sup>2</sup> Dale, H. H., and Dudley, H. W. The Presence of Histamine and Acetylcholine in the Spleen of the Ox and the Horse, *J. Physiol.* **68**: 97, 1929.

<sup>3</sup> Loewi, O., and Navratil, E. Ueber humorale uebertragbarkeit der Herznervnenwirkung, *Arch. f. d. ges. Physiol.* **214**: 678, 1926. Aeschlimann, J. A., and Reinert, M. Pharmacological Action of Some Analogues of Physostigmine, *J. Pharmacol. & Exper. Therap.* **43**: 413, 1931.

4 58 p m Hemorrhages were appearing on the surface

5 52 p m Up to this time the graft had been in a state of spastic contraction most of the time, with short periods of partial relaxation The surface appeared raw, it oozed blood and it was swollen and edematous The secretion had changed from a thick to a thin, watery mucus

Dog 15—*The results of experiments with acetylcholine and prostigmine*

6/13/37, 10 33 a m Solution of prostigmine (1 cc, 1:4,000) was given intravenously One per cent solution of acetylcholine bromide was applied every five minutes to the surface in doses of 0.2 cc during the next forty-five minutes

10 35 a m There was a severe spasm, with blanching of the surface

10 36 a m Petechial hemorrhages were beginning to appear on the surface With contraction of the surface, the graft blanched On relaxation there was immediate flushing of the graft The spasm of the muscles, both circular and longitudinal, in this case was sustained

10 45 a m The graft was beginning to appear swollen and edematous, and multiple hemorrhages were seen A tremendous amount of thick mucus had been secreted

10 52 a m A  $\frac{3}{8}$  inch (0.3 cm) layer of thick mucus was removed with forceps, care being taken not to touch the graft Many hemorrhagic streaks were seen in the mucus The graft looked as though it had been pounded

11 25 a m A biopsy specimen was taken Thin mucus had been secreted for the past fifteen minutes The graft was bloody on the surface

At the end of the period of application of acetylcholine, biopsy specimens of the grafts were taken for all 6 animals A photomicrograph of the mucosa from the explant in dog 14 is shown in figure 3 When compared with the normal explant (fig 1) the outstanding features were distention of the subepithelial vessels, with rupture in some places and bleeding onto the surface of the mucosa, absence of mucus from the cells, and loss of surface continuity of the epithelial cells in a number of places, with the formation of small erosions

### 3 EFFECT OF MUSCULAR CONTRACTION PRODUCED BY SHIGA DYSENTERY TOXIN

It has been shown by Reid, Anderson, Stubblefield and Ivy<sup>4</sup> that Shiga dysentery toxin produces severe enteritis when given intravenously to dogs and that the colon is most severely affected Ecker and his associates<sup>5</sup> noted that the intravenous injection of Shiga toxin and

4 Reid, P. E., Anderson, M. X., Stubblefield, H. I., and Ivy, A. C. Protective Action of Sodium Thiocyanate Against Dysentery Toxin (Shiga), *J. Infect. Dis.* **55** 112, 1934

5 Ecker, E. E., and Biskind, M. S. The Effect of Certain Toxic Substances in Bacterial Cultures on the Intestinal Movement II Effect of Filtrates of Young Cultures of the Colon-Typhoid Group of Organisms on the Intestinal Movement of Rabbits as Recorded by a New Cinematographic Method, Correlation of This Effect with the Production of Food Poisoning by Members of This Group, *Arch. Path.* **7** 204 (Feb.) 1929 Ecker, E. E., and Wolpaw, B. J. The Effect of Certain Toxic Substances in Bacterial Cultures on the Intestinal Movement IV The Production and Action of the Toxic Substances of *Bacillus Dysenteriae* (Shiga-Kruse), *ibid.* **10** 407 (Sept.) 1930

of filtrates from young cultures of *Bacillus paratyphosus* B caused increased tone or an increase in amplitude of contraction or both in the exteriorized intestine of rabbits. Experiments were undertaken to observe the effect of Shiga dysentery toxin on the colonic explant and to determine whether the damage produced might not be due to spasm of the muscles.

Accordingly, Shiga toxin was prepared from a four day broth culture by the method of Reid, Anderson, Stubblefield and Ivy<sup>4</sup>. Six animals (dogs 1 to 6), which had been used in the study of normal secretion of mucus, were employed in these experiments.

In the first group of experiments with dogs 1 to 3, toxin (filtrate A) was used from an organism which failed to grow on subculture. One cubic centimeter of filtrate was placed on the surface of each graft thirty minutes before each intra-

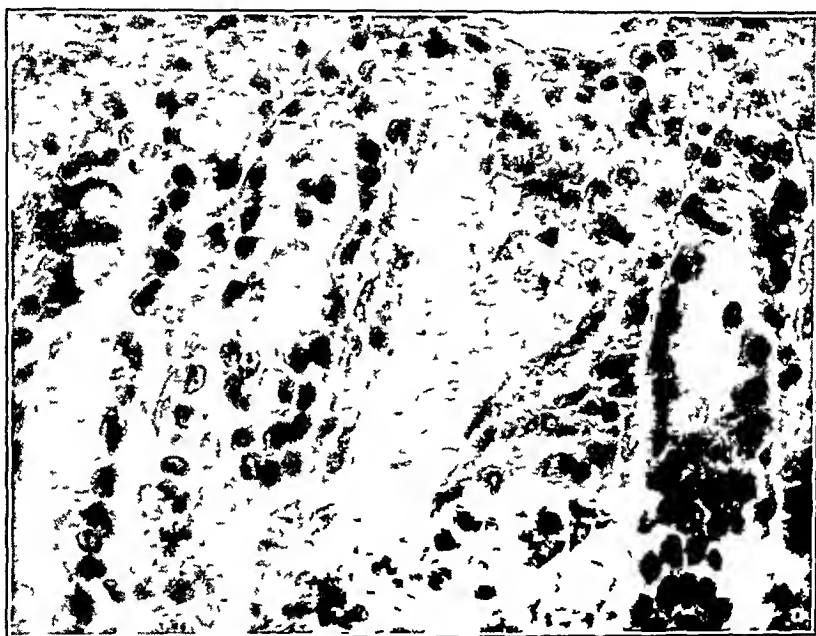


Fig 3—Photomicrograph ( $\times 400$ ) of a graft fifty-five minutes after the administration of prostigmine and acetylcholine chloride. Note the absence of mucus, the distention of the vessels and the loss of surface continuity. One capillary can be seen emptying directly onto the surface of the graft.

venous injection. There was no visible response of the graft after such an application. The filtrate was then given intravenously in doses beginning with 0.25 cc per kilogram of body weight, and the injections were continued thereafter, 0.5 cc per kilogram being given. In dogs 1 and 2 daily injections of toxin were given for five days. Dog 3 received injections every four days for five doses.

Dogs 1 and 3 showed the typical effect of intravenous injection—vomiting, diarrhea and bloody stools. About fifteen seconds after the toxin had been injected into these animals powerful spastic contractions developed in both the circular and the longitudinal fibers of the grafts. At brief intervals during the next twenty minutes the violent activity of the muscles was punctuated by slight relaxation. After this

the activity gradually subsided, and the graft was at rest an hour after the injection. Associated with the spasm was the appearance of edema and induration. Petechial hemorrhages were seen on the surface of the explant from five to seven minutes after the injection, and in twenty minutes much fresh blood was oozing from the graft. At first, thick mucus was secreted in abundance, but later this changed to a thin, watery secretion. On the day following an injection of toxin, the graft appeared red, hyperemic and edematous and showed punctate ulcers which had bled into the mucus on the dressing.

For dog 3 the injections were made several days apart, and for dog 1 injections were given daily. The effect was the same in these animals. Each successive injection led to severe spasm and a more rapid appearance of hemorrhage from the surface of the graft than at the previous injection. In dog 1 the graft returned to normal four days after the final injection, but in dog 3 nine days elapsed before the mucosal surface approached normal. The protocol on a series of injections given to dog 3 was as follows:

*Dog 3—Intravenous administration of Shiga dysentery toxin*

2/19, 4 53 p m Shiga toxin (5 cc) was given intravenously

4 55 p m Considerable spasm of the graft was noted

4 59 p m The graft relaxed occasionally but was contracted most of the time

5 00 p m Petechial hemorrhages began to appear on the surface

5 15 p m The graft was alternately relaxing and contracting, the contractile phase taking up three fourths of the time. There was considerable oozing of blood on the surface. The dog was having diarrhea with tenesmus. Small specks of blood were in the stools.

2/20 The graft was dressed and was found to be red and edematous. There were numerous petechial hemorrhages in the mucous covering. The dog had diarrhea, with bloody stools.

2/21 The dog had tarry stools, followed by tenesmus, during which drops of bright red blood appeared. The graft was in much better condition. Only a few hemorrhagic areas remained.

2/22 The graft was improving, being almost normal. The dog had loose stools, with old blood on the outside of the feces. Bright red blood appeared, with tenesmus at the end of defecation.

2/23 The graft appeared normal. Proctoscopic examination revealed a red, edematous mucous membrane with considerable hemorrhagic ooze from the surface. Several small ulcers were seen.

2 15 p m Shiga toxin (5 cc) was given intravenously. The graft became spastic at once, and petechial hemorrhages appeared in three minutes.

4 15 p m The dog had had loose, bloody stools, with much tenesmus, during the past one and one-half hours. The graft showed many hemorrhagic areas. The spasm had gradually relaxed.

2/25 Proctoscopic examination revealed a markedly inflamed mucous membrane which bled easily. A few small ulcers were seen.

2/28 The graft appeared normal.

8 48 p m Shiga toxin (5 cc) was given intravenously.



8 50 p m The graft showed spastic contraction of marked degree

8 51 p m There was considerable hemorrhagic ooze from the surface of the graft The dog was having severe tenesmus, with bloody dejecta

Concomitant with the changes in the graft were diarrhea, tenesmus and vomiting When the administration of the toxin had been omitted for several days, the consistency of stools gradually returned to normal, but blood showed on the surface At the end of the movement the dog continued to strain and would produce several drops of bright red blood and mucus This observation was made for both dog 1 and dog 3 on five successive days It seemed as if the act of defecation set up enough spasm in the irritated bowel to produce the bloody mucus at the end of the movement Proctoscopic examination of dogs 1 and 3 forty-eight hours after the injection of toxin revealed an inflamed, edematous mucosa, which bled freely when wiped with gauze Small ulcerations were seen throughout the entire segment of colon examined (12 cm)

In the third animal (dog 2), which received filtrate A daily, no spasm of the graft was seen, and there was only mild diarrhea, without blood in the stools This animal, however, vomited continuously and had formed tarry stools, which showed a strongly positive reaction to tests for occult blood Proctoscopic examination after the fifth injection of toxin revealed no abnormality in the colonic mucous membrane of this animal It was able to retain no food and only small amounts of fluid, it died ten days after the final injection At autopsy, several large ulcers were observed in the duodenum and jejunum which were the probable source of the occult blood in the stools Both the colon and the explant were normal on gross and microscopic examination

The second group of experiments was performed on 3 other animals (dogs 4 to 6), filtrate from another Shiga organism being used Both four (filtrate B) and ten (filtrate C) day cultures were used Filtrate B was given to dogs 4 to 6 in initial doses of 0.5 cc per kilogram of body weight, when this produced no effect, the dose was increased gradually up to 2 cc per kilogram Only transient diarrhea resulted There were no bloody stools, and the grafts did not show any increased muscular activity Filtrate C was given, with similar results Another Shiga strain was not available, so further experiments could not be conducted Biopsy material was not obtained, because the last experiments were unsuccessful

#### 4 EFFECT OF ISCHEMIA WITHOUT MUSCULAR CONTRACTION

Because of the possible action of muscular contraction in causing the lesions just described through secondary disturbances of circulation experiments were conducted in which local ischemia without muscular

spasm was produced. As has been shown by Drury and his associates,<sup>6</sup> the colonic explant blanches when the animal is under light ether narcosis. Three animals (dogs 4 to 6) were therefore given light ether anesthesia for a period of forty minutes in order to permit observation of the effect of ischemia on the explant. Although the blanching was pronounced and the muscles were relaxed, there appeared no edema, hemorrhage or secretion of mucus on the surface. Solution of posterior pituitary double U. S. P. strength was given intravenously to the same animals in 0.5 cc. doses. Marked blanching of the graft without muscular contractions was noted. The blanching was present intermittently over a period of one-half hour. Again no surface changes were observed.

#### COMMENT

The findings in these experiments may well help to explain some of the clinical facts about ulcerative colitis. When severe spasm of the colonic explants was induced by mechanical irritation, by parasympatheticomimetic drugs or by Shiga toxin, a markedly injurious effect on the mucosal surface resulted. An initial outpouring of mucus was followed by secretion of a more serous fluid at a time when the goblet cells of the mucosa were found to be empty. Hyperemia and hemorrhages into the mucosa were commonly observed, and ulcerations appeared in many instances. Over the area of these ulcers no mucus was secreted until healing had occurred. Even after apparent healing, the mucosa was more sensitive to trauma than normally. That these deleterious effects were not produced by ischemia secondary to muscular contraction is suggested by negative results of ischemia without muscular contraction produced by light ether narcosis and by solution of posterior pituitary.

If spasm is a prime factor in the causation of ulcerative colitis, one would expect to find pathologic changes in those parts of the colon with the most powerful musculature. The strongest muscles of the colon are in the rectum,<sup>7</sup> and elsewhere the strength of the tenial bands exceeds that of the circular fibers.<sup>8</sup> In 95 per cent of the patients with ulcerative colitis the disease commences in the rectum.<sup>9</sup> Its further

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6 Drury, A. N., Florey, H., and Florey, M. E. Vascular Reactions of the Colonic Mucosa of the Dog to Fright, *J. Physiol.* **68** 173, 1929.

7 Kirkes, W. S. *Handbook of Physiology*, ed. 16, Philadelphia, P. Blakiston's Son & Co., 1900.

8 Gleize-Rambal, L. Sur l'individualité anatomique du côlon descendant, *Compt. rend. Soc. de biol.* **99** 2015, 1928, **100** 368, 1929.

9 Rankin, F. W., Barger, J. A., and Buie, L. A. *The Colon, Rectum and Anus*, Philadelphia, W. B. Saunders Company, 1935.

development along the course of the most powerful muscles was well described by Virchow <sup>10</sup>

In particular it is the projections of the mucous membrane, caused by the anatomical distribution of the muscle tissue, which are affected by preference. Hence the especial susceptibility of the mucosa along the insertion of the three longitudinal muscle bands and of the transverse folds of the membrane.

In the last 2 patients with ulcerative colitis whom I have studied post mortem, the mucous membrane of the rectum was entirely denuded, and there were three streaks of denuded surface along the descending colon and sigmoid flexure. These lay directly over the tenial bands. There were other minute ulcerations appearing between the tenias. Their linear arrangement, corresponding to the direction of the circular muscle fibers, was striking.

That muscular spasm may lead to erosion of the mucosal surface of all portions of the intestinal tract, including the colon, is suggested by the observations of Light, Bishop and Kendall <sup>11</sup>. These investigators produced acute gastric ulcers in rabbits by placing pilocarpine hydrochloride in the subarachnoid space. In 7 cases the stomach was observed directly. It contracted severely as soon as the drug was given and continued its intermittent spastic contractions for two hours. Although these authors attributed the changes primarily to ischemia and secondarily to digestive action of the gastric juices, the observations made in the present investigation suggest that spasm was the primary factor in producing the results.

In further support of the importance of muscular spasm in the production of ulcers in the intestinal tract was the appearance of duodenal and jejunal ulcers in 1 of the animals (dog 2) that was given potent dysentery toxin. In this animal the ulcers may well have been produced by spasm of the upper portion of the intestine, just as the ulcerations in the graft and colon of dogs 1 and 3 were the result of muscular hyperactivity.

Admittedly, in all patients with ulcerative colitis the process does not commence in the rectum, and some have areas of so-called focal colitis elsewhere in the large bowel <sup>11a</sup>. In such cases it is possible that localized spasm has developed in one section of the colon without involvement elsewhere. Supportive evidence for this contention is

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10 Virchow, cited by Flexner, S., and Sweet, J. E. *The Pathogenesis of Experimental Colitis and the Relation of Colitis in Animals and Man*, *J. Exper. Med.* 8 14, 1906.

11 Light, R. U., Bishop, C. C., and Kendall, L. G. *The Response of the Rabbit to Pilocarpine Administered into the Cerebrospinal Fluid*, *J. Pharmacol. & Exper. Therap.* 47 37, 1933.

11a Lum, R., and Porter, J. E. *The Distribution of Lesions in Ulcerative Colitis and Its Possible Significance*, *Am. J. Path.*, to be published.

found in the appearance of ulcerative lesions in the colon above an obstruction. For example, in 1 patient who had carcinoma of the recto-sigmoid region, the muscles were hypertrophied and contracted immediately above this lesion, and the mucous membrane overlying them was almost completely denuded. Below the obstruction, however, the mucous membrane was normal. It seems reasonable to suppose that spasm of the muscles would occur above but not below the obstruction and so may have determined the location of the ulcerations in the mucous membrane.

In considering certain well known clinical features of ulcerative colitis, further evidence is found suggesting that muscular spasm may play a role in initiating the process. At least early in the disease, the shortened, narrow colon commonly seen on roentgen examination is due to spasm, for Rankin, Barger and Buie<sup>9</sup> have presented evidence that such a "pipe stem" colon can be returned to normal by medical treatment. Patients with this disease are usually high strung and react with excessive sensitivity to their environment. It is common knowledge that nervousness will produce diarrhea, and this may well develop to the point where the colon is in an almost constant state of spasm.

An original attack of bacillary dysentery has been found by several authors to precede the development of ulcerative colitis.<sup>12</sup> Recently Felsen<sup>13</sup> has argued strongly for bacillary dysentery as a frequent precursor of ulcerative colitis. The observations of Ecker and his associates<sup>5</sup> and the experiences reported in this paper show that the intravenous injection of Shiga toxin produces violent muscular contractions. Although other authors have postulated a specific injurious effect of the dysentery toxin on the mucosal cells, it has been shown in the present investigation that the severe injury resulting from intravenous injection of toxin was entirely similar to the result obtained when muscular spasm was produced by mechanical irritation or by the use of parasympathomimetic drugs. That the toxin does not act as a specific poison to the epithelial cells was well shown by the negative response of the mucosal surface to direct application of the toxin.

If, then, the colon is an organ which can produce much self injury simply by its own overactivity, once this mechanism is set in motion, the experiments reported here further suggest how a vicious cycle of pathologic changes may become established. The normal protective action of mucus was plainly shown by the fact that after twenty-four hours, when a layer of mucus had formed on the surgical dressing,

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12 Hurst, A. F. Ulcerative Colitis, Excluding Tropical Diseases, *Lancet* **1** 636, 1931. Thorlakson, P. H. T. Ulcerative Colitis, *Canad. M. A. J.* **19** 656, 1928.

13 Felsen, J. Relationship of Bacillary Dysentery to Distal Ileitis, Chronic Ulcerative Colitis and Nonspecific Intestinal Granuloma, *Ann. Int. Med.* **10** 645, 1936.

no further secretion of mucus occurred. During the early stages of induced muscular hypermotility in the explants, a layer of thick mucus was secreted, but this gradually changed to a thin, watery type of secretion. Microscopic sections showed complete absence of goblet cells in the mucous membrane. That the fecal stream may well injure the epithelial cells once the secretion of mucus becomes deficient is shown by the observations on the effect of mechanical stimulation on the explant. A light wipe with gauze removed the film of mucus from the surface without causing bleeding, while a similar wipe applied immediately afterward caused bleeding from the mucosa.

Presumably, when the intact colon is stimulated to hyperactivity, the supply of mucus becomes exhausted, and the epithelial cells are no longer protected from the irritation of the passing fecal stream. Moreover, in the present experiments it was noted that when ulcers formed, mucus was not secreted by the ulcerated areas until healing had occurred. Even after return to a normal appearance, the regenerated colonic epithelium was found to be far more susceptible to mechanical injury than normal epithelium. Such observations indicate elements which further contribute to the chronicity of pathologic processes in the colon after the initial injurious effect of muscular spasm.

It is possible that a deficiency of mucus might be the primary factor in certain cases of ulcerative colitis. Tilden and Miller<sup>14</sup> produced ulcerations in the colon of monkeys with a diet deficient in vitamin A. Other investigators<sup>15</sup> have shown that vitamin A is essential for the normal function of mucus-secreting cells in the gastrointestinal tract. That such deficiency of mucus encourages ulcer formation is also demonstrated by experiments with menthol<sup>16</sup>. This substance depletes the store of glycuronic acid, which is a necessary substance for the production of mucus. When the depletion is complete, ulcerations and inflammatory reaction are found along the gastrointestinal tract.

Degenerative lesions of the mucosa of the gastrointestinal tract have been found in diseases in which deficiency of some portion of the vitamin B complex is suspected—pernicious anemia, pellagra and sprue<sup>17</sup>. Similar deficiencies have been demonstrated in instances of chronic ulcerative

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14 Tilden, E. B., and Miller, E. G., Jr. Response of the Monkey to Withdrawal of Vitamin A from the Diet, *J. Nutrition* **3** 121, 1930.

15 Richards, M. B. Role of Vitamin A in Nutrition, *Brit. M. J.* **1** 99, 1935.  
Cramer, W., and Kingsbury, A. N. Local and General Defense Against Infections, and the Effect on Them of Vitamin Deficiency, *Brit. J. Exper. Path.* **5** 128, 1924.

16 Manville, I. A. The Interrelationship of Vitamin A and Glycuronic Acid in Mucine Metabolism, *Science* **85** 44, 1937.

17 Mackie, T. T., and Pound, R. E. Changes in the Gastro-Intestinal Tract in Deficiency States, with Special Reference to the Small Intestine. Roentgenologic and Clinical Study of Forty Cases, *J. A. M. A.* **104** 613 (Feb. 23) 1935.

colitis,<sup>18</sup> and although usually regarded as secondary to the intestinal disturbances, they could certainly contribute to the chronicity of the process. Thus several factors, all of which are effective in initiating damage to colonic mucosa, may begin the vicious cycle of spasm, mucus exhaustion, damage to the surface structures and further spasm which is essential to the production of the final picture of ulcerative colitis.

### SUMMARY

Colonic explants in dogs react to various stimuli by a spastic contraction of the musculature. Whether this spasm is produced by mechanical stimulation, parasympatheticomimetic drugs or dysentery toxin, its result is damage to the overlying epithelial structures, with hemorrhage and ulceration.

The mode of action of dysentery toxin in producing ulcerations of the mucosa is thus apparently through the injurious effects of muscular spasm.

Secretion of mucus is immediately increased in association with muscular contraction of the explant. When hyperactivity of the muscles continues, only a thin, watery material, inadequate for protective purposes, is secreted.

Ulcers are not covered with a coating of mucus until they have healed, thus, presumably, in the intact colon they are constantly exposed to trauma from the passing fecal current.

Even after a return to a normal gross appearance, the regenerating epithelium is more sensitive to trauma than normal epithelium of the colonic graft.

Ulcerative colitis may be conceived as a specific reaction to a number of influences which can initiate spasm of the colonic musculature. These include possible hyperactivity of the parasympathetic nervous system, infections such as dysentery, and vitamin deficiency. Once the colon becomes spastic, it is potentially an organ that can produce severe damage to its own surface structures. The exhaustion of the secretion of mucus, together with nutritional deficiency, may contribute to prevent healing of the colon. That muscular spasm may be responsible for lesions of the mucosa of other portions of the gastrointestinal tract is suggested by certain of the present experiments as well as by a reinterpretation of the work of others.

Dr S. Maddock furnished the animals and materials used in these experiments. Dr W. B. Castle gave advice regarding the preparation of the manuscript. Facilities for the making of the photomicrographs were made available by Dr C. K. Drinker. The preparation of the sections used in these studies and their interpretation were the work of Dr J. Porter, of the Mallory Institute of Pathology.

<sup>18</sup> Mackie, T. T. *Ulcerative Colitis*. II. The Factor of Deficiency States, *J. A. M. A.* **104**: 175 (Jan. 19) 1935.

# ABNORMALITIES OF CALCIUM METABOLISM

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Faulty calcium metabolism accounts for a wide range of discomforts and disabilities and in some of its forms leads to untimely death. There have been enough interest and effort on the part of chemists, research workers and clinicians to improve the efficiency of the treatment of patients with this disorder.

Calcium is deservedly a central figure in mineral metabolism. Americans ingest too little calcium salt. The body does not naturally conserve calcium. In fact, if there is a shortage in the supply of calcium or if there is an increased demand for it, e. g., during pregnancy, excretion proceeds without economy, and the organism is confronted with progressive deficiency.

Oversupply of calcium is probably never a practical problem in human beings. In those persons with abnormal deposits of calcium salt, the problem is one of perversion of distribution and not one of excessive intake.

A series of experiences in the field of calcium metabolism has prompted this report. The following case records, presenting a variety of clinical patterns, may help to clarify some phases of the subject.

## REPORT OF CASES

### CASE 1—*Calcinosis universalis*

The patient, a man aged 20, was well until July 1927, when fever developed and there was soreness in all the accessible muscles. Some of the muscles became swollen and there was marked limitation of articular motion because of the swelling and soreness. He became drowsy and passed an excessive amount of urine. In this uncomfortable state he entered the Alameda County Hospital where he was thought to have rheumatic fever. He was given salicylates. He was not much improved when discharged to his home.

A year later he reentered the hospital with the same symptoms plus contractures of the joints of the arms and legs. In 1929 two years after the onset, a nodule developed on the medial side of the left knee joint, and a few months later another one developed symmetrically over the right knee joint. Biopsy showed that one of these contained calcified inflammatory tissue (fig 1). Similar nodules developed at various points, including the elbows, the flexor surface of one meta-

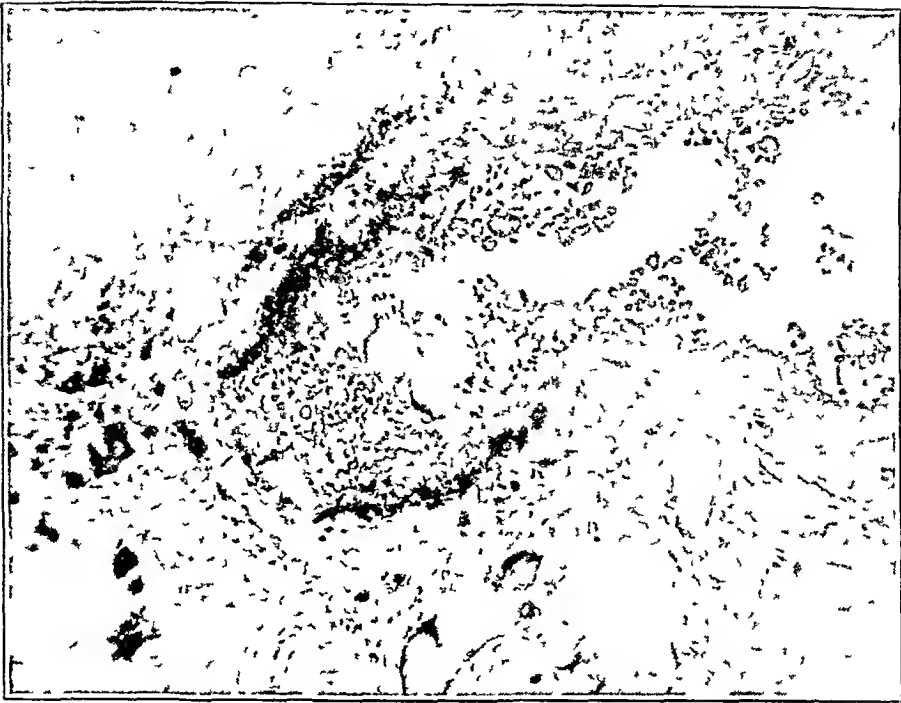


Fig 1 (case 1)—Calcinosis universalis Microscopic section of a biopsy specimen from a nodule on the knee joint Note the hyalinization of stroma, with areas of foreign body reaction manifested by giant cells, macrophages and fibroblasts The homogeneous small and large masses are calcium phosphate

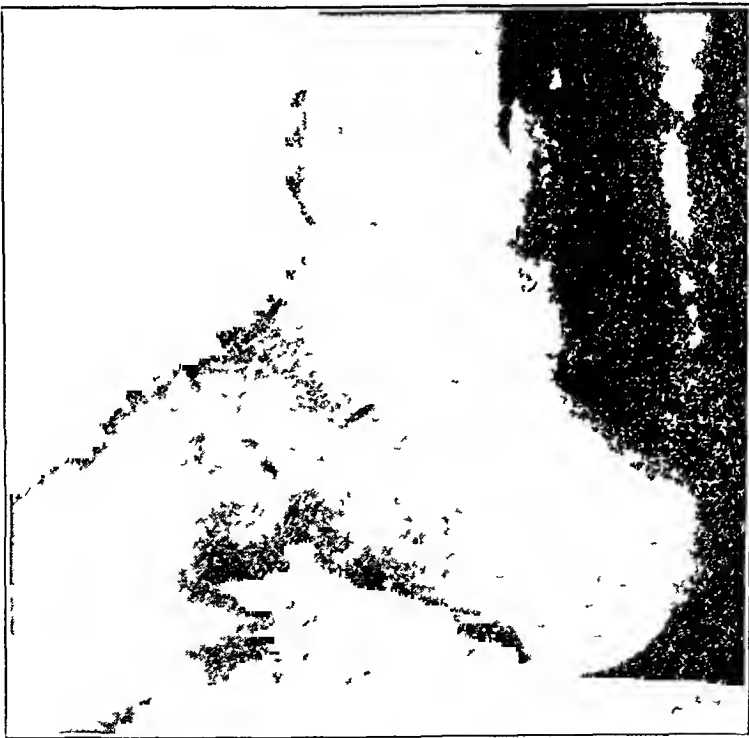


Fig 2 (case 1)—A roentgenogram of the ankle and heel, showing demineralization of the bone, with increased trabeculation Note the deposition of calcium in the achilles tendon



carpal bone, the medial side of the right humerus and both heels. These nodules were palpable, and roentgenograms showed infiltration with calcium (figs 2 and 3).

With the passage of time there was increased calcification. Treatment was symptomatic. A ketogenic diet, which made the  $p_H$  of the urine 5.2, may have caused a slight remission of symptoms.

This patient was studied extensively at the University of California Hospital and at the Cowell Memorial Hospital as well as at the Alameda County Hospital. He weighed only 115 pounds (52 Kg). His height was approximately 5 feet and 9 inches (175 cm). Emaciation was marked. His blood pressure was 120 systolic and 80 diastolic. Other physical findings were not significant. The com-

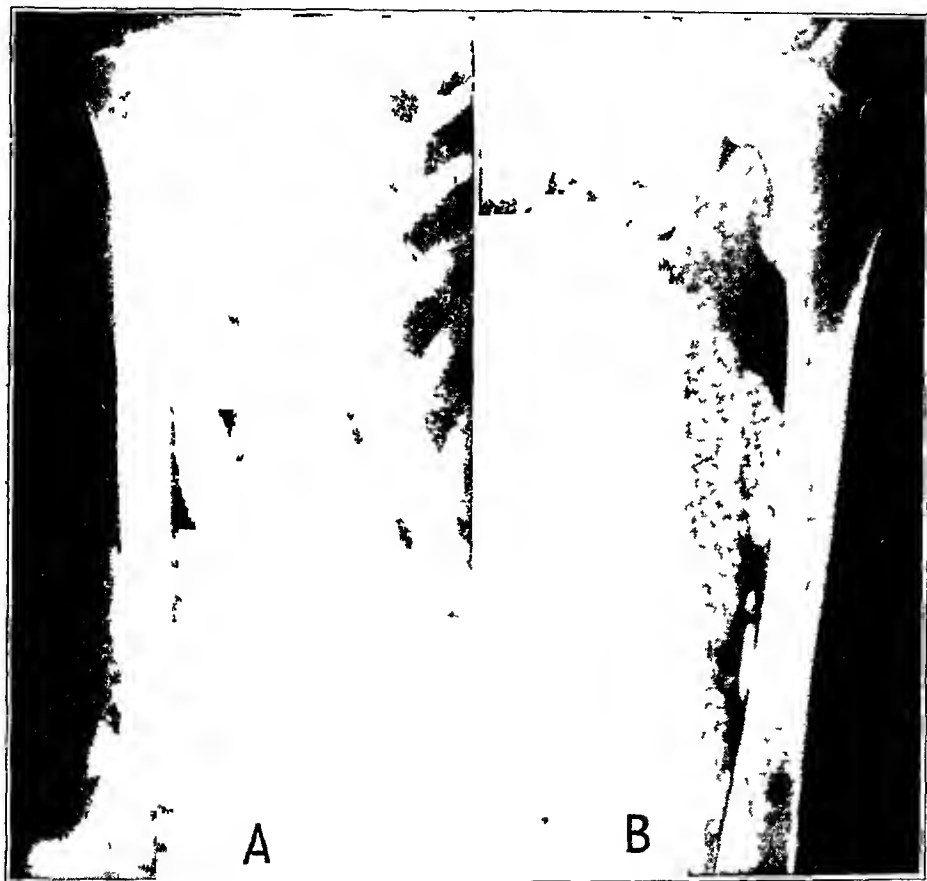


Fig 3 (case 1)—*A*, the shoulder girdle and humerus, showing some patchy demineralization, with scattered depositions of calcium in the soft tissue. *B*, the lower portion of the pelvis and femur, showing patchy demineralization, with massive calcification in the muscles of the thigh.

plete blood count was normal. The quantities and ratio of albumin and globulin in the serum were normal. Studies of the total calcium balance showed nothing abnormal. The carbon dioxide-combining power of the blood plasma was 61.5 volumes per cent. The  $p_H$  of the blood was 7.5.

*Comment*—The normal quantities of calcium and phosphorus in the serum, the normally available carbon dioxide and the moderate increase in the alkalinity of the blood were probably not concerned with this

picture of abnormal deposition of calcium Oscar Klotz<sup>1</sup> considered this condition in 1905 He explained that a poor blood supply and lessened viability of the cells result in the formation of a succession of alkali soaps, with final deposition of calcium soap

Scleroderma is often associated with calcinosis, and the histologic changes in the skin in cases of scleroderma have been shown by Epstein<sup>2</sup> to be stages in a process of calcification Langmead<sup>3</sup> has shown that in cases of myositis fibrosa and dermatomyositis also suggestively similar pathologic pictures are presented

The late Dr Campbell Howard<sup>4</sup> said he believed that thyroid therapy helped 2 of his patients with scleroderma We tried a ketogenic diet, thinking to mobilize calcium from its abnormal sites, as in the case reported by Kennedy,<sup>5</sup> but without clinical benefit There is no treatment which is dependably successful<sup>6</sup> Flooding the patient with sodium biphosphate has sometimes been beneficial<sup>7</sup> A deposit of calcium about the joints is sometimes removed by hyperemia induced by heat<sup>8</sup> Even normal bone becomes rarefied if it is made hyperemic<sup>9</sup> Acidosis and local hyperemia may help in the resolution of early calcium deposits in some cases

#### CASES 2 AND 3—*Renal rickets*

Two patients with renal rickets were studied in the laboratory of the Children's Hospital of the East Bay No single patient available to us presented all the characteristic findings of this disease but a composite picture of these 2 patients is informative The term rickets is misleading, because renal rickets is not a vitamin deficiency disease Renal rickets is the result of nephritis with poor excretion of phosphates

1 Klotz, O Studies upon Calcareous Degeneration, J Exper Med 7 633, 1905

2 Epstein, N N Calcification of the Skin and Subcutaneous Tissues, Arch Dermat & Syph 28 510 (Oct) 1933

3 Langmead, F S The Relationship Between Certain Rare Diseases, Arch Pediat 40 112 (Feb) 1923

4 Howard, C P Personal communication to the authors

5 Kennedy, R L J Calcinosis and Scleroderma Treatment of a Case by Use of the Ketogenic Diet, in Collected Papers of the Mayo Clinic and the Mayo Foundation, Philadelphia, W B Saunders Company, 1933, vol 24, p 1087

6 Rothstein, J L, and Walt, S Calcinosis Universalis and Calcinosis Circumscripta in Infancy and Childhood, Am J Dis Child 52 368 (Aug) 1936

7 Craig, J, and Lyall, A A Case of Calcinosis Universalis and a Suggested Method of Treatment, Brit J Child Dis 28 29 (Jan-March) 1931

8 Hitchcock, H H Calcium Deposits About Joints, West J Surg 45 353 (July) 1937

9 Orton, G H Calcium Changes and Their Importance in Diagnostic Radiology (Mackenzie Davidson Memorial Lecture), Brit J Radiol 9 102 (Feb) 1936

The first patient was a girl of 6 years who had always been smaller than normal. She was in fair health until a few weeks before her terminal illness. Then she suddenly had a convulsion and after that had excess urine, headache, nausea and vomiting. She had hypertension (130 systolic and 90 diastolic) two weeks before her death. This blood pressure reading was fairly representative of the period of acute illness. The urine contained large amounts of albumin. Only 10 per cent of the phenolsulfonphthalein injected intramuscularly was excreted in the urine in two hours. The nonprotein nitrogen content of the blood was 150 mg per hundred cubic centimeters just prior to her death in uremia.

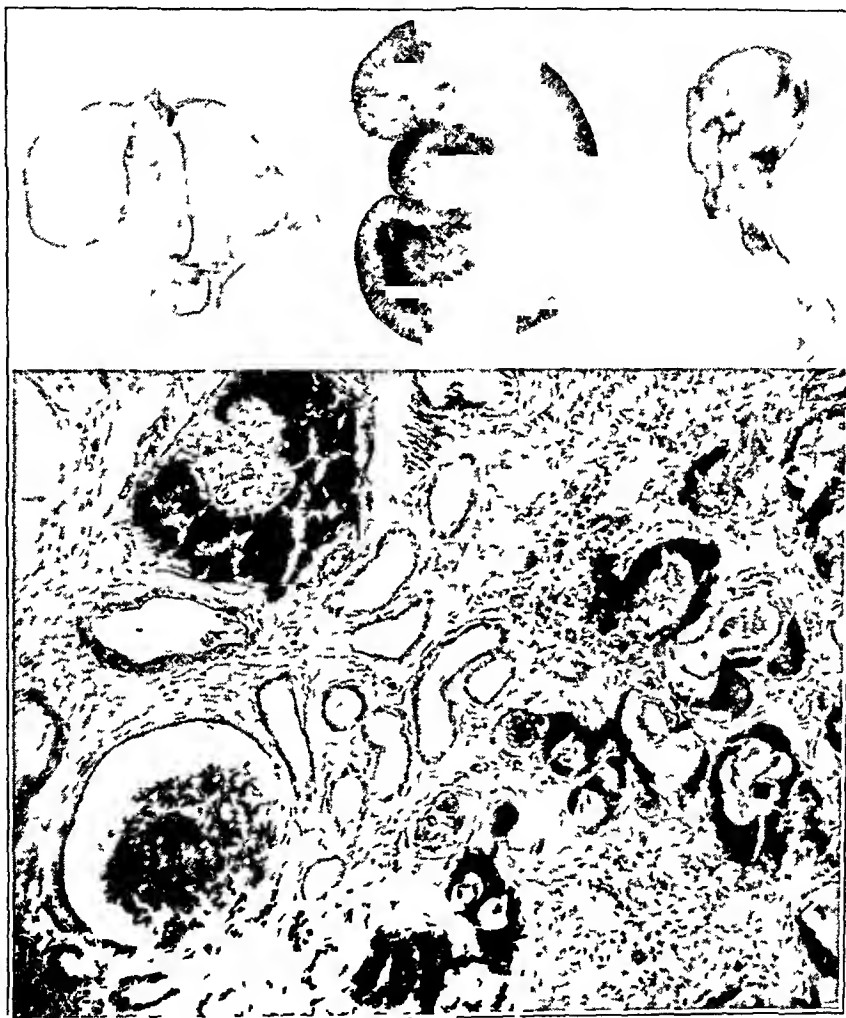


Fig 4 (case 2) —Renal rickets. Necropsy specimens of the kidneys and a normal kidney from a child of the same age for comparison. Note the marked hypoplasia. Microscopic sections of the defective renal tissue showed sclerosis and scattered areas of calcification.

Partial autopsy showed general infantile development. Figure 4 shows the kidneys compared with a kidney from a normal child of the same age. The former were markedly atrophic with loss of all normal markings. The sections demonstrated pronounced interstitial fibrosis with little functioning renal tissue (fig 4). The glomeruli were included in the sclerotic process.

The second case was that of an 11 year old boy. He was also smaller than normal and throughout life showed deficient development. For a year prior to his terminal illness he had polyuria and failing vision. He had an occasional headache. During that year he had several convulsions. Studies of the blood and urine gave findings similar to those in case 2. The eyegrounds showed edema and many areas of hemorrhage. The blood pressure was about 200 systolic and 150 diastolic for two weeks before death. Roentgenograms showed diffuse osteoporosis of the long bones, with uneven rarefactions at the ends, which were later found to be islands of immature cartilage. The skull showed granular porosis associated with thickening of the cortex, causing a ground glass appearance (fig 5). The calcium content of the blood was 8.8 mg and the phosphorus content 5 mg per hundred cubic centimeters about two weeks before death.

The autopsy confirmed the roentgenographic findings in the bones. There was no parathyroid adenoma. The heart was large, firm and fibrous and contained many areas of calcification. Microscopic study confirmed the gross examination



Fig 5 (case 3)—Renal rickets. A roentgenogram of the skull, showing thickening of the cortex and the ground glass appearance of the bone.

(fig 6). The kidneys were small, firm and granular. The cortex of the bones was thin where examined, and cross sections showed fibrous change, with scattered areas of cartilage and round cell infiltration.

*Comment*—Osseous changes similar to those here reported occur in 40 to 50 per cent of these cases and when present practically establish the diagnosis.<sup>10</sup> The phosphorus content of the blood is high because of poor excretion of phosphorus by the damaged kidneys. Our second patient had a low calcium value, being especially low with relation to the value for phosphorus. L. G. Parsons<sup>10</sup> explained the situation as follows. In the usual case of renal rickets the calcium content is not

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10 Parsons, L. G. Bone Changes Occurring in Renal and Coeliac Infantilism, and Their Relationship to Rickets. I. Renal Rickets, *Arch Dis Childhood* **2**: 1 (Feb.) 1927, II. Coeliac Rickets, *ibid* **2**: 198 (Aug.) 1927.

extremely low, but it is always low in proportion to the phosphate content. This disproportion between the values for calcium and phosphorus acts to disturb the growth of bone. The renal function varies. The excretion of phosphorus fluctuates, and deposition of bone is defective because of the change in the tides of phosphorus and calcium. There is another element that is disturbing to osseous growth, since the poor renal function makes for acidosis, which may also deter deposition of bone.<sup>11</sup>

There are two possible reasons why our second patient had convulsions. First, there was uremia, and, secondly, there was the low calcium content of the serum. The headaches, vomiting and ocular

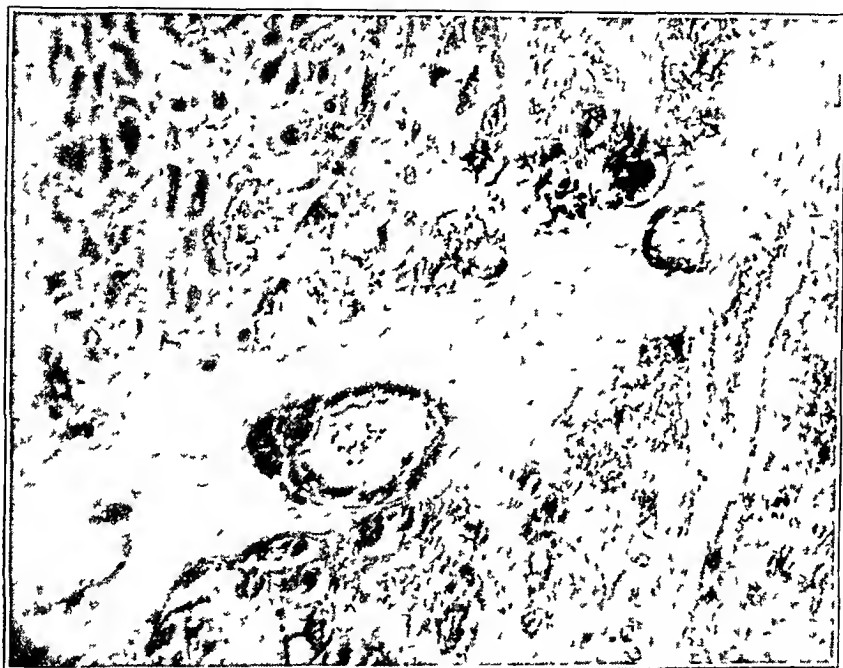


Fig 6 (case 3) —A microscopic section of the heart, showing marked degeneration of the cardiac fibers, with numerous vacuoles. The dark-staining areas are aggregations of calcium. Note the marked fibrosis and round cell infiltration.

changes probably represented the approach toward uremia. As in our patients, marked deficiencies of height and weight are frequent in this disease.

This type of rickets results from excess phosphate and insufficient calcium in the blood plus acidosis in the presence of growing bone. Sometimes there are remissions because of improved renal function, with better excretion of phosphates. Remissions and exacerbations of the rickets usually occur because of spontaneous variations in renal func-

11 Parsons, L. G. Rickets and Allied Diseases, *Lancet* 2:485 (Sept 8) 1928.

tion, but eventually the patient dies of uremia before the age of 20 years. Parsons<sup>10</sup> has warned against using ultraviolet irradiation in these cases. He has inferred that the result is increased absorption of phosphate from the bowel and disproportion between the values for phosphorus and calcium.<sup>11</sup> If this concept is correct, vitamin D, should, in general, be withheld in the presence of renal rickets.

CASE 4—*Fragilitas ossium* ("hereditary hypoplasia of the mesenchyme" of Key)

A girl aged 7½ years had had fractures since the age of 18 months. She first fractured the left leg below the knee then an arm and then had various other fractures and sprains, all of which healed slowly. She had shown retarded mental and physical development. Various treatments had been tried by different attending physicians. One gave parathyroid extract for two months but the patient became weaker and was said to have become mentally unstable. Other consultants increased the calcium and vitamins in her diet.

Her mother had a pronounced deformity of the vertebral column, the diagnosis being *fragilitas ossium*. Both the mother and the patient's maternal half-sister had blue scleras.

When first seen the child looked sick, had a pasty complexion and a thick skin, was queer acting and had slow association of ideas. The scleras were abnormally blue. The teeth had irregular surfaces. The muscle tone was poor and as a consequence there was sagging of weight-bearing structures, resulting particularly in lumbar lordosis and exaggerated pronation of the left foot. Roentgenograms showed diffuse rarefaction of bone (fig 7). Physical and roentgen examination showed good union at the old sites of fracture.

The basal metabolic rate was +3 per cent. The calcium content was 10 mg and the phosphorus content 21 mg per hundred cubic centimeters of blood before treatment. After treatment with liberal amounts of calcium, phosphorus and viosterol, the calcium content remained about the same, but the phosphorus content rose to 45 mg per hundred cubic centimeters.

A surprising improvement was noted when she was seen three months after this treatment was started. There was great improvement in weight, health, mental activity and well-being. She had gained 10 pounds (4.5 Kg) in the first two months of therapy. She had become energetic. School work had been difficult before, but afterward she had actually led her class in scholarship. She had had several falls without fracturing any bones. Such falls might in previous times have resulted in fractures.

The treatment was empiric and included the administration of a preparation composed of dicalcium phosphate and "bone phosphates" and also of a compound containing calcium, phosphorus and magnesium salts.<sup>12</sup> Egg yolk, milk and meat were emphasized in her diet. Ten drops of viosterol in oil (containing 10,000 U S P units of vitamin D per gram) was given to her daily. Because of her definite improvement with this program, we believe that there may have been a real therapeutic effect, whether or not due to the rise in the phosphorus content of the blood.

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12 These two preparations were, respectively, "bone salts" (Upjohn) and "phytin" (Ciba).

*Comment*—General considerations in regard to this problem have been outlined by Bromer<sup>13</sup> and by Key<sup>14</sup>. The underlying cause is deficiency in the function of osteoblasts, and, as in several of the malacic diseases of bone, there is excess phosphatase in the serum<sup>15</sup>. Though the bones look rarefied in the roentgenograms and are soft and fragile, the quantity and proportion of calcium and phosphorus in them are



Fig 7 (case 4)—Fragilitas ossium. This roentgenogram of the tibia and fibula is typical of the roentgenograms obtained in cases of fragilitas ossium. There is diffuse osteoporosis, which is more pronounced in the diaphysial portions. There is marked thinning of the cortical bone. The epiphyses are normal and show no pathologic change. There is a fracture in the lower portion of the tibia.

13 Bromer, R. S. Osteogenesis Imperfecta, *Am J Roentgenol* **20** 631 (Nov) 1938.

14 Key, J. A. Brittle Bones and Blue Sclera, *Arch Surg* **13** 526 (Oct) 1926.

15 Cantarow, A. Calcium Metabolism and Calcium Therapy, Philadelphia, Lea & Febiger, 1933. Mitchell, A. G. Nephrosclerosis in Childhood, with Special Reference to Renal Rickets, *Am J Dis Child* **40** 101 (July), 345 (Aug) 1930.

normal,<sup>13</sup> and the amounts of mobile calcium and phosphorus in the blood serum are also usually normal. It is as if there were ample building material for bone but a poor arrangement of that material by the osteoblasts, with fragile structures resulting. Endocrine influences are speculative only. Some children with this disease improve spontaneously during adolescence.<sup>16</sup> The finding of a low phosphorus content of the serum of our patient and the improvement with forcing of phosphorus may be worth considering in other similar cases.

#### CASE 5—*Parathyroid adenoma*

A 45 year old woman was seen in a short terminal illness only. Although the clinical data are incomplete, the cause of her death and the autopsy data warrant this account. She entered the hospital in December 1934, suffering from a fractured femur which had resulted from a fall. The fracture and the roentgenographic appearance of the bone are shown in figure 8A. While in bed, with the injured leg in an extension appliance, she was shifting her weight with the aid of a hand trapeze when suddenly the left side of the thoracic cage collapsed. There were nine fractures on that side, as shown roentgenographically. She died several days later as a result of pulmonary collapse and the pneumonia which followed. The only medical information obtained from prior consultants was that her basal metabolic rate had been normal and she had had some type of anemia when examined a year previously.

Roentgenograms showed diffuse demineralization of all the bones studied, including the skull, thorax, arms, pelvis, hips, foot and one ankle (fig 8). There were numerous fractures, including those of the hip and ribs, which occurred just before death.

Postmortem examination showed a thin woman with delicate features, thick glossy hair and tapering fingers. Some of the recent fractures were observed directly, and there was no evidence of healing. She had no obvious exophthalmos.

The thyroid and parathyroid glands are shown in figure 9. The thyroid gland weighed 80 Gm. It was firm, meaty and hyperplastic, both grossly and microscopically. The acinar epithelium showed definite infolding and feathering, as observed in the microscopic sections. There were also moderate fibrosis and some round cell infiltration. There was a thyroid adenoma, which measured 2 by 3 cm. In the right posterior region was a parathyroid adenoma, the shape of an egg, which measured 2 by 3 cm. It was somewhat fluctuant and cystic and contained a sanguineous fluid. The adenoma was yellowish, and its wall varied from 2 to 5 mm in thickness. There was only one other parathyroid gland, the left inferior one, it showed a normal size and shape. The microscopic sections of the parathyroid adenoma showed some fibrosis, interstitial hemorrhage and a typical parathyroid structure, with definite hyperplasia (fig 9B). The bones generally were soft and cut easily. The ribs could be sectioned with ordinary shears. They showed complete replacement by fibrocartilaginous tissue. The right adrenal gland was moderately hyperplastic, and the left one was markedly so. It was approximately four times larger than normal. Microscopic study of the larger adrenal gland showed the hyperplasia noted grossly but no other significant abnormality. The hyperplasia was most marked in the cortex.

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16 Hills, R. G., and McLanahan, S. Brittle Bones and Blue Scleras in Two Generations, *Arch Int Med* 59:41 (Jan) 1937.



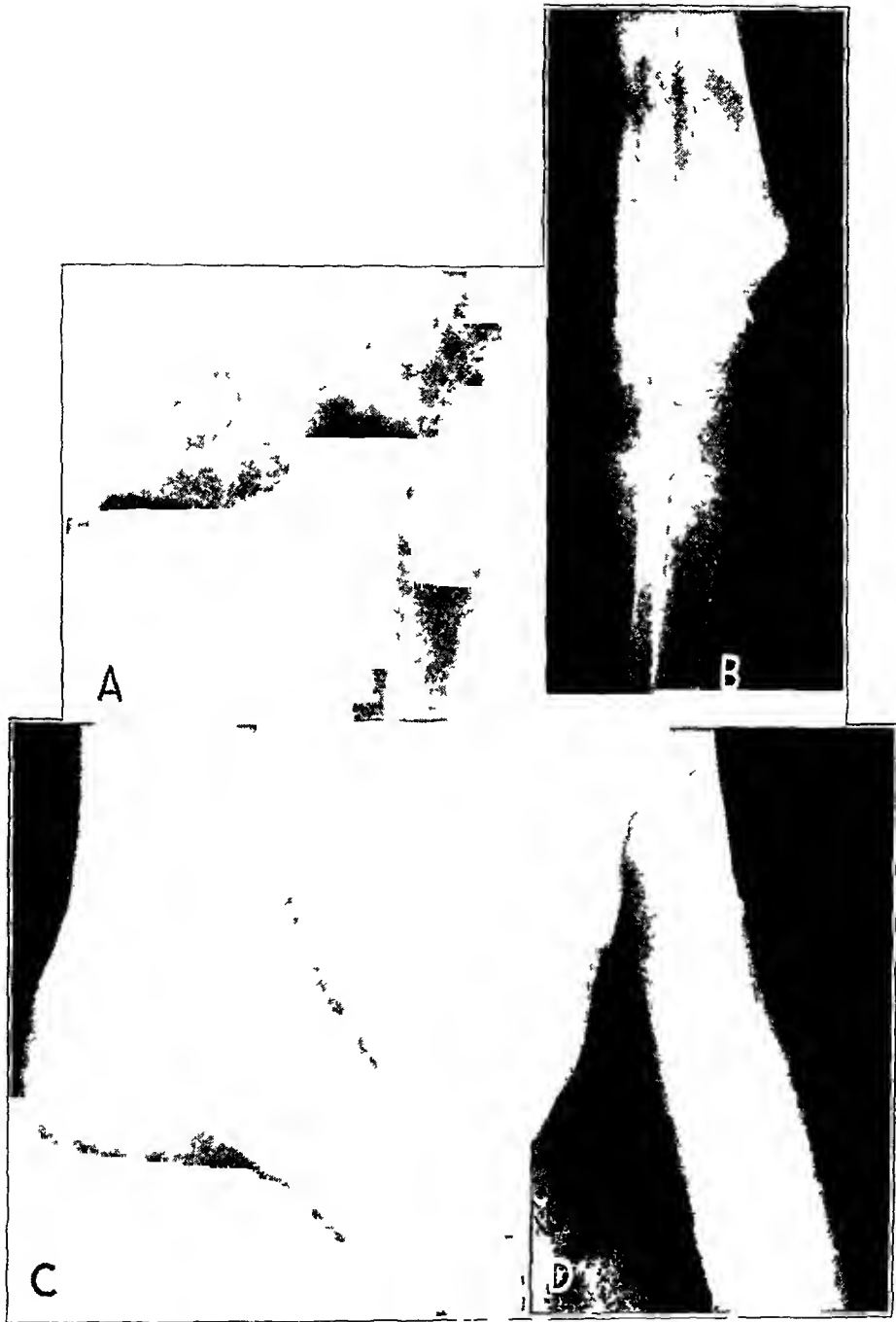


Fig 8 (case 5) —Parathyroid adenoma, with hyperplasia of the thyroid and adrenal glands *A*, a roentgenogram of a portion of the pelvis and femur, displaying diffuse demineralization and fracture of the neck of the femur. Note the absence of cyst formation, which is usually seen in cases of uncomplicated hyperparathyroidism *B*, a view of the knee, showing demineralization. There is no fracture *C*, a view of the foot and ankle, showing demineralization *D*, diffuse demineralization of the humerus, with fracture of the upper third, which occurred spontaneously



Fig 9 (case 5) —*A*, a posterior view of the thyroid gland, showing the parathyroid adenoma set off by an oblong white background (autopsy specimen) Note the diffuse enlargement of the thyroid gland due to hyperplasia The parathyroid adenoma is yellow, discrete and encapsulated, having undergone central cystic degeneration The separate mass to the left is an adenoma of the thyroid gland *B*, a microscopic section of the parathyroid adenoma, showing diffuse hyperplasia, with moderate interstitial fibrosis There are a relative decrease in the cells of the acidophilic type and a relative increase in the basophilic cells

The diagnoses included the following parathyroid adenoma, thyroid hyperplasia, thyroid adenoma and hyperplasia of the adrenal glands

*Comment*—Most patients with hyperparathyroidism show cystic changes in the bone. This patient showed diffuse demineralization, and this change may conceivably have resulted from the combined effects of the parathyroid adenoma and thyrotoxicosis<sup>17</sup>. The decalcification of thyrotoxicosis is diffuse.

The pituitary gland should have been inspected at autopsy. Basophilic adenoma of the pituitary gland is associated with osteoporosis. It is also associated with hypertrophy of the adrenal cortex<sup>17</sup>. Was there pituitary basophilism in addition to the hyperthyroidism and the parathyroid adenoma to account for the astounding softening of the bones in this case?

There is no need to review the various characteristic findings in cases of hyperparathyroidism. The observations of Shelling<sup>18</sup> and of Barr<sup>19</sup> are valuable for reference.

*CASE 6—Diffuse bony metastases from a renal cell carcinoma*

In the fall of 1935 a 60 year old physician was seen because of a variety of complaints. He had pain in the lower portion of the back, lassitude, mental confusion, anorexia and palpitation. Roentgenograms showed diffuse rarefaction of the bones in the lower portion of the back and moderate decalcification of the sternum and ribs. There was nothing clinically to suggest thyrotoxicosis, an occasional cause of diffuse demineralization of bones. Parathyroid overactivity was suspected. The calcium content of the serum was 16 mg and the phosphorus content 3.2 mg per hundred cubic centimeters. Study of the calcium balance proved that there was an actual calcium deficit. There was a negative balance of 3,474.8 mg in five days of study.

Date	Intake, Mg	Output in Urine, Mg	Output in Feces, Mg
Oct 20	302	100	717
21	135	38.3	1,015
22	245	38.3	1,015
23	496	25.1	1,047
24	325	25.1	1,047
Totals	1,503	136.8	4,841

These findings strengthened the suspicion of parathyroid overactivity. There was no abnormal mass in the parathyroid region. The possibility of aberrant parathyroid tissue in a normal position or in the mediastinum was strong enough.

17 Zondek, H. *Diseases of the Endocrine Glands*, Baltimore, William Wood & Company, 1935. Aub, J. C., Bauer, W., Heath, C., and Ropes, M. *Studies of Calcium and Phosphorus Metabolism. Effects of Thyroid Hormone and Thyroid Disease*, J. Clin. Investigation 7: 97 (April) 1929.

18 Shelling, D. H. *The Parathyroids in Health and Disease*, St. Louis, C. V. Mosby Company, 1935.

19 Barr, D. P., and Bulger, H. *The Clinical Syndrome of Hyperparathyroidism*, Am. J. M. Sc. 179: 449 (April) 1930.

to warrant exploration. The patient was referred to Drs Henry Christian, Joseph Aub and Edward D Churchill, at the Peter Bent Brigham Hospital, Boston.

Twelve years before this illness he had had surgical removal of the left kidney for renal cell carcinoma. No symptom or sign suggested any recurrence of this except that the possibility of metastasis to the bone was casually considered. It was thought unlikely that there would be recurrence or metastasis after twelve years of health following this first surgical treatment.

When Dr Churchill explored for abnormal parathyroid tissue, nothing of pathologic significance was found. The patient died eleven days after operation. At autopsy a recurrence of renal cell carcinoma was seen at the operative site, and metastasis of the neoplasm to rarefied bones was proved.

*Comment*—In this case the pain in the lower portion of the back was attributed to metastatic neoplasm seen at autopsy, with no necessary correlation with the perverted calcium metabolism. The lassitude and mental confusion probably depended on more than one cause. The patient was toxic and sometimes had moderate fever. He was a nervous person, and the toxemia may have caused the mental changes, in whole or in part. But the abnormally high calcium content of the blood may also have contributed to these effects, as is suggested by the behavior of a boy who had an overdose of parathyroid extract.<sup>20</sup> His "palpitation" was variable. One electrocardiogram showed a rate near 30 per minute, with normal complexes, another showed absolute arrhythmia at a rate near 100 per minute, with auricular fibrillation. An abnormally high calcium content of the serum may have caused each of these cardiac variations. A high calcium level has been reported to depress the sino-auricular node, but it also predisposes to ectopic beats.<sup>21</sup> The anorexia may have been due to toxemia or a high calcium content<sup>20</sup> or both.

Although in this patient calcium was probably assimilated normally and deposited satisfactorily in the bones, some of the bones were giving up calcium to the blood stream too rapidly because of the malignant bony metastases. The roentgenograms showed diffuse rarefaction of the bones (fig 10).

In cases of parathyroid disease the rarefaction is usually cystic, and the loss of calcium is in the urine rather than in the stool.<sup>22</sup> Our patient's rarefaction was not cystic, and he lost relatively little calcium in the urine. Was the rarefaction due to an overactive thyroid gland? This is unlikely, because he did not have hyperthyroidism clinically and, again, the loss would have been principally by way of the urine.<sup>23</sup> Was

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20 Lowenberg, H., and Ginsburg, T. M. Acute Hypercalcemia, *J. A. M. A.* 99:1166 (Oct 1) 1932.

21 Sampson, J. J., and Anderson, E. M. The Treatment of Certain Cardiac Arrhythmias with Potassium Salts, *J. A. M. A.* 99:2257 (Dec 31) 1932.

22 Aub, J. C. The Importance of Calcium Metabolism in Internal Medicine, *Proc. California Acad. Med.* 1:74, 1930.

23 Aub, J. C. Calcium and Phosphorus Metabolism, in *Harvey Lectures (1928-1929)*, Baltimore, Williams & Wilkins Company, 1930, p. 151.

it due to disuse? Probably not, because with complete confinement in bed one would expect a more uniform rarefaction than the roentgenograms showed. These queries are valuable with respect to the corrected point of view made possible by the autopsy data on malignant involvement of bone.

This report is included because of the antemortem quandary and the postmortem answer and because of the interesting effect that a high calcium content of the serum may have on the function of soft tissue.



Fig 10 (case 6)—Metastatic carcinoma from primary renal cell carcinoma. Marked generalized osteoporosis is present. The osteoporosis is not typical of hyperparathyroidism and is more marked than that usually noted in a normal patient of this age. A generalized osseous metastatic carcinoma was present at postmortem examination.

#### CASE 7—*Senile osteomalacia*

In July 1931 a 65 year old woman, who worked as a maid in a hospital, fell to a sitting position and immediately had pain in the upper lumbar region of the spine. She was found to have a compression fracture of the first lumbar vertebra. All vertebrae visible in the roentgenograms showed decalcification. After months of orthopedic care she was gradually moved from bed, but with weight bearing, several other vertebrae became compressed, and her back was intolerably painful. More orthopedic measures followed, and medical investigation revealed the fact that in ten days she lost 7 Gm more calcium than she received in her food. This loss was probably not due to a digestive fault, because the stools contained almost

no fat and she had no diarrhea. Calcium and phosphorus were present in normal amounts in the blood. It was therefore assumed that there was some difficulty in fixing or retaining calcium in the bones, and treatment was directed with that possibility in mind. In order to be sure of an adequate supply of these elements she was given increased amounts of calcium and phosphorus in the food, in the form of milk and eggs. She was given lactose in order to favor absorption<sup>24</sup>. She was also given 0.5 cc of viosterol in oil three times daily (a total of 60,000 U S P units per day) for six months. In order to decrease lysis of bone by parathyroid hormone, the parathyroid region was irradiated four times at intervals of one week, with 430 roentgens given at 200 kilovolts with a 0.75 mm copper filter (about 200 roentgens on each side). Another study of the calcium balance was carried out during this period of therapy, as outlined, about two months after the last roentgen treatment, and it was found that she then retained calcium. In twelve days she excreted 0.5 Gm less calcium than she took in her food. After this she was again gradually moved from bed, this time with success. She was seen one year after this period of orthopedic care and confinement in bed and reported that

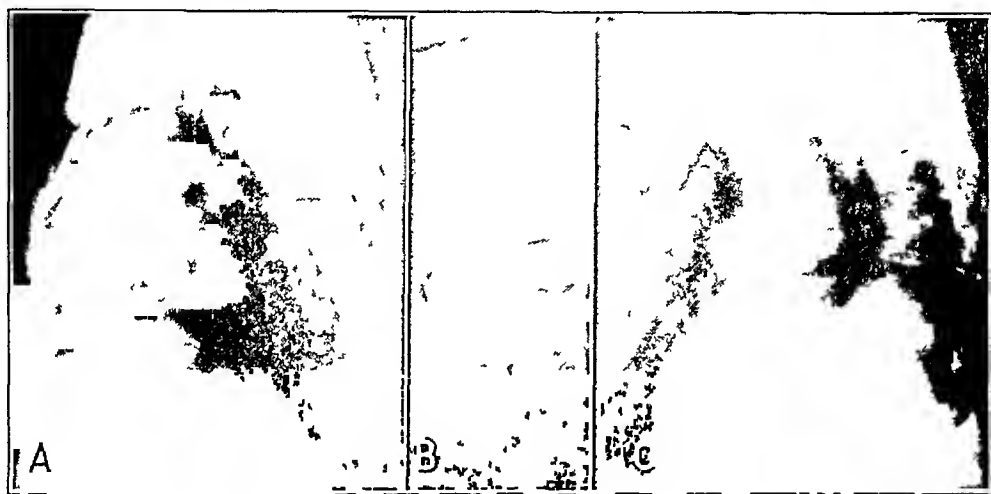


Fig 11—Senile osteomalacia. *A*, a lateral view of the patient's spine prior to treatment. *B*, a lateral view of the spine of a person of the same sex and age as the patient (an attempt was made to use an identical technic). *C*, a lateral view of the patient's spine after two years of treatment.

she was doing light housework without interruption. She required no orthopedic support of any sort. Roentgenograms of the vertebrae showed slightly more density than previously (fig 11).

Collateral findings were not of significance except that she had moderate hypertension and moderate sclerosis of the retinal vessels. There was nothing to suggest hyperthyroidism. The basal metabolic rate was +3 per cent. There was no palpable parathyroid tumor and, as mentioned before, the calcium and phosphorus levels of the blood were normal.

*Comment*—Patients with this type of disorder are numerous and usually do not improve with treatment. Clinical improvement in this case was undoubted. The roentgenograms and the quantitative study

<sup>24</sup> Bergeim, O. Intestinal Chemistry. Carbohydrates and Calcium and Phosphorus Absorption, *J Biol Chem* **70** 35 (Sept) 1926.

of the calcium are subject to error and fallacy, despite attempts to make the comparisons quantitatively accurate. The amounts of viosterol given were suggested by success in the treatment of intractable rickets with large doses<sup>25</sup> and by some of the experimental work of Shelling, in which small doses of vitamin D caused poor calcification of bone, larger doses, hypercalcification, and still larger doses, decalcification<sup>26</sup>. We might now hesitate to give these amounts<sup>27</sup>. A physician of this community died, with polyuria, weakness and anorexia, after taking 2,500,000 U S P units daily for seventeen days<sup>28</sup>.

CASE 8—*Tetany in an adult*

In April 1929, during rounds of the wards at the Alameda County Hospital, an intern called attention to a patient whose principal complaint was of diarrhea. She was a nervous, inadequate person, weighing only 83 pounds (37.6 Kg) and being 5 feet and 4 inches (162.5 cm) tall. The principal pathologic findings were hypochromic anemia, achlorhydria, poor nourishment, poor posture and nervousness. She was discharged from the hospital. Five months later she called for help at her home because of muscular cramps.

She presented a dramatic physical picture of tetany. Her mouth was dry, and the muscles were so stiff that she could scarcely talk. The upper eyelids were retracted. The arms were rigidly straight, the hands dorsally flexed on the forearms and the fingers tightly clenched. All accessible muscles were involuntarily tense. The legs were stiff and straight, and the feet were in ventral flexion, so that they almost continued the straight line of the leg. The Chvostek and Trousseau signs were not at first obtainable, presumably because of extreme rigidity, but later they were elicited, when treatment had resulted in some relaxation. This condition had come on gradually for several days. She was greatly and justifiably frightened. Her muscles pained, and she was thoroughly aware of the progression of her condition. Two cubic centimeters of parathyroid extract was injected intramuscularly, and she was sent back to the hospital. After arrival there she was given calcium chloride intravenously and rapidly lost the discomfort due to the tetany. The calcium content of the blood was 5.3 mg per hundred cubic centimeters.

She was given a diet low in roughage. Sedatives and camphorated tincture of opium were administered in order to control the diarrhea. She was given food which provided large amounts of calcium, together with 15 grains (0.97 Gm) of calcium lactate three times per day. Thirty drops of diluted hydrochloric acid and 5 drops of viosterol were taken with each meal. Ten cubic centimeters of 5 per cent solution of calcium chloride was injected intravenously three times during the first three days. She began improving symptomatically with the first

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25 Jampolis, M, and Londe, S. Need of Larger Doses of Viosterol in Severe Rickets (Osteomalacia Type). Comparative Study of Efficiency of Viosterol and Cod Liver Oil, *J A M A* **98** 1637 (May 7) 1932.

26 Shelling, D H, and Asher, D E. Calcium and Phosphorus Studies. Relation of Calcium and Phosphorus of Diet to Toxicity of Viosterol, *Bull Johns Hopkins Hosp* **50** 318 (May) 1932.

27 Reed, C I. Symptoms of Viosterol Overdosage in Human Subjects, *J A M A* **102** 1745 (May 26) 1934. Leake, C D. Vitamin D Toxicity, *California & West Med* **44** 149 (March) 1936.

28 Kerr, W W. Personal communication to the authors.

dose After eight days the calcium content of the serum was 8 mg per hundred cubic centimeters, and eleven days later it was 10 mg per hundred cubic centimeters Exposures to a quartz mercury vapor lamp were used During a stay of two months in the hospital she gained consistently in weight and well-being She has had no recurrence of tetany in the six and one half years since her discharge

At present her general condition is better She now weighs consistently about 105 pounds (47.6 Kg) Diarrhea returns at times but is usually controlled by the use of 25 drops of diluted hydrochloric acid with meals plus  $\frac{1}{2}$  grain (0.03 Gm) of phenobarbital once or twice daily She had been able to work and to support herself during most of the time since her discharge from the hospital Nervousness and diarrhea constitute a menacing sequence at times The calcium content of the serum one year after her acute attack was 10.4 mg per hundred cubic centimeters She has taken calcium lactate or calcium gluconate (30 grains [1.94 Gm] per day) and viosterol (10 drops per day) at various times since her acute illness

A roentgenogram of the gastrointestinal tract showed nothing of interest except that the colon was redundant The stool showed one or two fat droplets per high power (dry) field and no protozoa A roentgenogram of the hand showed normal density of the bones A determination of the phosphorus content of the blood was made The value was 2 mg at a time when the calcium content was 8 mg per hundred cubic centimeters The basal metabolic rate was —17 per cent An alcohol test meal showed no free hydrochloric acid A blood count showed hypochromic anemia

*Comment*—It is our impression that this patient had a fault in the absorption of calcium through the intestinal wall and that diarrhea was a possible factor therein Lack of gastric hydrochloric acid may have contributed by favoring the diarrhea and by decreasing the solubility of the calcium in the lumen of the intestine This patient suffers from nervous hypertension, and an imbalance of the vegetative nervous system may have contributed to the diarrhea Reassurance and sedation probably helped in this respect

The gastric anacidity and diarrhea may also have contributed to the anemia, and the anemia may have been on a nutritional basis even with an adequate menu The net result of an inadequate diet or an adequate diet poorly absorbed may be the same A normal intake of food, the use of reduced iron and also the better availability of calcium probably united to help the anemia <sup>29</sup>

The injection of parathyroid extract at the height of the tetany was not ideal treatment, since this drug has a four hour period of latency Calcium chloride should have been given intravenously and was used soon afterward Viosterol was given to furnish vitamin D, which is said to improve absorption of calcium <sup>11</sup> Lactose was used to help the absorption of calcium also <sup>24</sup>

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29 Orten, J. M., Smith, A. H., and Mendel, L. B. Relation of Calcium and of Iron to Erythrocyte and Hemoglobin Content of Blood of Rats Consuming Mineral Deficient Ration, *J. Nutrition* **12** 373 (Oct) 1936



We assume that this patient had poor absorption of food and metabolites and that this was due to (a) the abnormally rapid motility of the digestive content and (b) the lack of gastric hydrochloric acid. Of interest is the fact that she was one of twins. She had rickets as a child, and her sister, with an identical menu, did not. Also there was a history of soreness of the tongue, peeling of the fingers and melancholia along with diarrhea in 1927. The diagnostic impressions were tetany, achlorhydria, hypochromic anemia, undernourishment, class D posture, preexisting rickets and pellagra, suspected from the history.

CASE 9—*Paget's disease (osteitis deformans)*

The patient was a 52 year old man. Two years before entry he first noticed pain and discomfort in the right knee and leg on walking. One and one-half years before entry the legs were noticeably bowed, and he had a moderate limp. Some of his bones felt sore when he was lying in bed, and the bones of the legs hurt when he walked.

His health had been good until the present symptoms began. Since that time he had gradually become more and more incapacitated. There was a history of malaria and typhoid many years before entry. He was 5 feet and 10 inches (177.8 cm) tall and weighed 155 pounds (70.3 Kg). Systematic general examination revealed nothing abnormal except bony changes. Roentgenograms showed rarefaction, deformity and density (figs 12 and 13). The measurements of the right and left legs were equal.

No significant abnormality of the vascular system was found. The laboratory reports on the blood were as follows:

	Protein, Mg per 100 Cc	Calcium, Mg per 100 Cc	Phosphatase, Bodansky Units per 100 Cc	
March 11, 1937	2.2	11.3	43.5	(normal upper limit near 7 units)
April 30, 1937	3.9	10.7		
Aug 30, 1937	3.3		65.0	

Renal calculi were not suggested by the history, examination of the urine or roentgenograms.

Deep application of heat by radiotherapy lessened his pain. He improved symptomatically with a diet high in calcium. Neither of these measures can be considered specific.

*Comment*—This case report is included because there was a malacic disease of the bone. There was a lowered calcium content in the involved bone.<sup>30</sup> An abortive form of osteitis fibrosa cystica may be confused with Paget's disease. Active osteitis fibrosa cystica is usually associated with an abnormally high calcium content and low phosphorus content of the serum. In both cases there is an abnormally high phosphatase content of the plasma, Paget's disease being accompanied by a higher average content than osteitis fibrosa cystica. A high phosphatase content of the

<sup>30</sup> Kay, H. D., Levy-Simpson, S., Riddoch, G., and Vilvandré, G. E. Osteitis Deformans, with Roentgenologic Section, *Arch Int Med* 53:208 (Feb) 1934.

plasma is characteristic of several malacic diseases of bone. It is probably a result rather than a cause of Paget's disease<sup>31</sup>. The probable principal function of phosphatase is to liberate inorganic phosphate from phosphoric esters, making inorganic phosphorus available for bone formation. In the malacic diseases of bone the phosphatase is truant. There is a

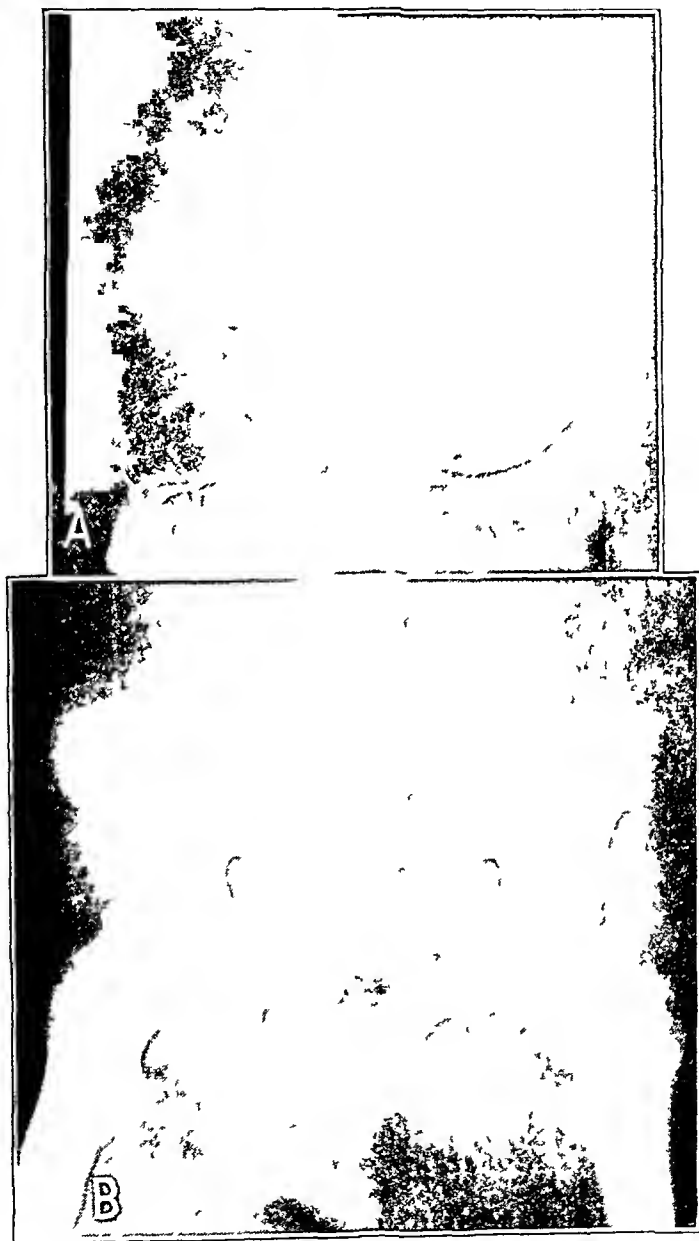


FIG 12 (case 9) —Paget's disease. *A*, a roentgenogram of the skull. Note the large, irregular rarefaction in the left frontal bone, in the pattern described as that of osteomalacia circumscripta. *B*, a roentgenogram of the pelvis and femurs. Note the diffuse rarefaction of the right ilium, the various zones of rarefaction elsewhere and the increased width of the right ilium.

31 Cantarow, A. Review of Phosphatase Activity and Calcium and Electrolyte Metabolism, *Internat Clin* 1 230 (March) 1936

low content of it in the bone, with an increased amount in the plasma<sup>32</sup> There is no successful treatment for Paget's disease Many practical details were noted by Gutman<sup>32</sup> in a review of 116 cases Irradiation may ease local pain, but remissions of symptoms are common and improvement after treatment may not be due to the treatment



Fig 13 (case 9) —Paget's disease Roentgenograms showing bowing of the softened, weight-bearing femur, with secondary thickening of the cortex due to osteitis

#### COMMENT

From these widely separated clinical experiences, the calcium metabolism of the organism is viewed from a variety of positions Some of the complex relations of the minerals in human metabolism are studied at the bedside

One should suspect disturbance of mineral metabolism when there is defective nutrition A child of subnormal stature may have congenital renal insufficiency, with a fault in the excretion of phosphate, as in renal rickets A thin woman with diarrhea may be losing calcium, to the disadvantage of the function of the soft tissues, tetany may develop A poorly nourished person with anemia may have poor absorption of iron or of calcium from the digestive tract The food eaten may contain too little of these elements

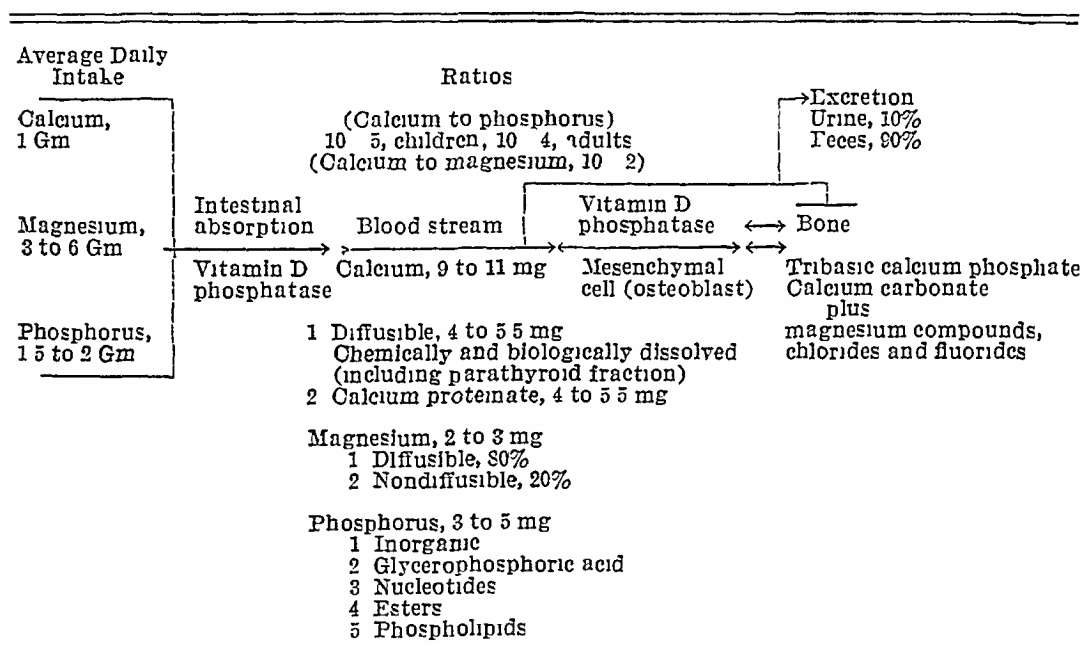
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32 Gutman, A B, and Kasabach, H Paget's Disease (Osteitis Deformans) Analysis of One Hundred and Sixteen Cases, *Am J M Sc* **191** 361 (March) 1936

Unusual fractures may be due not only to primary or secondary neoplasm in bones but to poor internal economy of calcium or of phosphate. A parathyroid adenoma or parathyroid hyperplasia may be the cause. Poor functioning of the osteoblasts may be the reason for the presence of rarefied bones which fracture too easily, as in case 4 (fragilitas osseum). There may be a lack of ability to deposit available calcium in bone, as we presume to be the case in senile osteomalacia.

A tonic convulsive state may be due to a lowered calcium content of the serum, as in our extremely tetanic patient. Convulsions may result from both uremia and low calcium values, as was possible in the case of our patients with renal rickets.

*Metabolic Sequences of Alkali Earth Metals*



A high calcium content may cause or predispose to an abnormally slow cardiac rate or to rapid, irregular cardiac action. Both effects were postulated in our patient with a high calcium content secondary to metastatic carcinoma of bone. If long sustained, the high calcium value may cause precipitation of calcium salts in soft tissue, as in the cardiac muscle in case 5 (parathyroid adenoma). The occurrence of renal and ureteral stone under like circumstances is a matter of considerable current comment.

Not all spurious deposits of calcium salt are traceable to overabundance of calcium in the blood. In calcinosis and several allied diseases the calcium and phosphate contents of the serum are normal. For some reason there are points of diminished tissue viability in these patients. Defective local circulation may be the reason. These regions become progressively buried in calcium salt.

In cases in which bone is abnormally calcified phosphatase is often present in the serum to excess. Phosphatase frees inorganic from organic phosphate for use in bone building. One would suppose, then, that when bone is deficient in calcium phosphate the body must be trying to provide excess phosphatase and thus encourage the deposit of calcium phosphate. But the increased supply does not always reach its goal in large quantity. In Paget's disease, phosphatase is present in the bone in less than normal amount.

When there is a suspicion of deranged mineral metabolism, the important facts can usually be obtained at the bedside with the aid of the laboratory and roentgenographic facilities in a class A hospital.

Some of the facts of human mineral metabolism are recorded in the accompanying table.

# RENAL AMYLOIDOSIS

A FURTHER STUDY OF THE CLINICAL COURSE AND PATHOLOGIC  
LESIONS IN FIFTY-SEVEN CASES

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AND

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In 1935 we<sup>1</sup> reported on 16 patients with renal amyloidosis for whom a clinical diagnosis had been made during life and had been verified by postmortem examination. These patients had been observed by us over a period of two to eight years, their records were reviewed and the data were tabulated with regard to the type of tuberculosis in which renal amyloidosis occurs, the likely precipitating factors, the urinary findings and renal function, the blood pressure, the physical findings and the condition of the eyegrounds, together with pertinent necropsy data and information regarding the distribution of amyloid in the kidney. In this way we attempted to portray the clinical life history in cases of renal amyloidosis as it occurs among patients with tuberculosis.

In this paper we are reporting on 41 additional patients with renal amyloidosis. Five of these belong to the aforementioned group, making a total of 21 patients for whom the clinical diagnosis of renal amyloidosis was confirmed at postmortem examination. The remaining 36 were those for whom a clinical diagnosis was not made during life, for the following reasons: (1) oversight and inadequate follow-up study, (2) a confusing clinical picture and findings, (3) our inexperience and an insufficiently high threshold of suspicion in the beginning of our study and (4) findings not sufficient for a clinical diagnosis of renal amyloidosis. This series comprises a total of 57 patients with pathologically proved amyloidosis. It is our purpose to analyze these cases in order to add to the clinical picture, to call attention to certain features about the disease that were probably overemphasized by us and to comment on the reasons for our failure to make a proper clinical diagnosis when this

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1 Altnow, H O, Van Winkle, C C, Maly, H W, and Williams, L E  
Renal Amyloidosis, Arch Int Med 56:944 (Nov) 1935

occurred and was avoidable. We are also presenting herewith a diagnostic schema which, we believe, will be of considerable aid in the earlier recognition of the less advanced stages. Since this paper supplements the data of our first publication, the same form of presentation will be used.

In the accompanying tables the 21 patients for whom the diagnosis was made and confirmed at postmortem examination are segregated as group 1 and the 36 patients for whom we failed to make the diagnosis, for one reason or another, as group 2.

In table 1 the data for the 57 patients show the nature of the cases of tuberculosis in which renal amyloidosis is found. Forty-seven patients had far advanced pulmonary tuberculosis, 4 had moderately advanced pulmonary tuberculosis and 6 had Pott's disease without pulmonary tuberculosis. One patient with far advanced and 1 with moderately advanced pulmonary tuberculosis had Pott's disease, and 1 with far advanced pulmonary tuberculosis had tuberculosis of the bones of the legs, making a total of 9 patients with tuberculosis of the bones (15.7 per cent).

Suppurating foci were present in the following cases: empyema, 7; Pott's disease, 8; tuberculosis of long bones, 1; draining sinuses from tuberculous kidney, 1; and tuberculous peritonitis with draining sinuses, 1. Eighteen patients, or only 31.5 per cent, showed suppurating foci. If cavitation of the lung is so considered, then each of the patients had a suppurating focus.

The outstanding complication was tuberculous enteritis. A clinical diagnosis based on symptoms and suggestive roentgen findings was made in 33 instances, but 13 of these diagnoses were not verified by postmortem examination. However, in 5 of these cases, amyloid infiltration of the intestinal wall was present. We believe that amyloid infiltration may produce gastrointestinal symptoms that simulate tuberculous enteritis. If only pathologically verified cases are considered, the incidence of tuberculous enteritis was approximately 60 per cent, and if amyloid infiltration of the intestine is added (which includes all cases in which there was a pathologic basis for the symptoms), the incidence was 70 per cent. A clinical diagnosis based on gastrointestinal symptoms, namely, an unexplained inability to gain weight, anorexia, nausea, flatulence, alternating constipation and diarrhea, and intermittent or persistent diarrhea, associated with cramping pain in cases of more advanced involvement, and suggestive roentgen findings was made in 57.5 per cent of the cases. Enteritis was present in 82 per cent, if unverified clinical cases (8), amyloid infiltration of the intestine (5) and pathologically proved cases (34) are included.

Tuberculosis of the appendix occurred in 16 of 51 patients, or in 31 per cent (6 had prior appendectomy). It was present 4 times inde-

pendently of tuberculosis of the intestines, and in 3 of these instances a diagnosis of enteritis had been made. Tuberculosis of the appendix may have been responsible for the production of the symptoms that led to the clinical diagnosis of enteritis.

The clinical diagnosis of rectal tuberculosis was made 9 times, confirmed in 3 cases and discovered at necropsy in 2 instances.

A clinical diagnosis of tuberculous laryngitis was made in 15 cases and discovered post mortem in another case. The rectum and larynx were not routinely examined post mortem.

Enlargement of the lymph glands sufficient for the clinical diagnosis of adenitis occurred 6 times, but enlarged lymph glands in regions inaccessible clinically were observed at necropsy 45 times, or in 79 per cent of the cases.

Pleural effusion was recognized by clinical methods 12 times and tuberculous pleuritis once. In 3 of these cases the effusion disappeared before death. Seven of these patients were considered as having empyema, and 1 was considered as having healed empyema. Thirteen additional patients showed effusion post mortem which had not been recognized by clinical methods. Active pleural involvement was therefore present in 26 patients (46 per cent). Tuberculous pericarditis was found at necropsy in 9 instances. A clinical diagnosis of tuberculous peritonitis was made in 1 case, but in 14 additional cases it was discovered at postmortem examination. Thirty-six patients, or 65 per cent, showed pleuritis, pericarditis or peritonitis alone or in combination, with the diagnosis established by either clinical or postmortem examination or both. This figure serves to emphasize the fact that tuberculosis of the serous membranes is an important complication.

Tuberculous infection of the kidney was present in 12 patients, and 10 showed other renal lesions (table 1).

#### PROBABLE PRECIPITATING COMPLICATIONS

There were 46 patients for whom the date of the presumptive or definite onset (or both) could be determined with reasonable accuracy (table 2). An outstanding clinical event or complication that might be associated with the onset of renal amyloidosis occurred 25 times (54 per cent), contrasted with an incidence of 87 per cent in the 16 cases formerly reported. This can probably be accounted for by the fact that in the patients in this group the onset was generally more insidious and the clinical picture less fully developed. The onset of clinical enteritis as a probable precipitating factor also became less conspicuous.

#### ALBUMINURIA

Ten patients showed no albuminuria, but for 2 the period of observation was short. In 47 patients with albuminuria the average duration



TABLE 1—Primary Lesions and Suppurating Foci, with Complication Noted Clinically and at Autopsy, Exclusive of Amyloidosis \*

[illegible]



TABLE 2—*Clinical Events and Onset of Renal Amyloidosis*

Group	Case	Date	Clinical Event	Date of Presumptive Onset of Amyloidosis	Date of Definite Onset of Amyloidosis
1	1	Dec 1924	Tuberculous laryngitis		
		July 1925	*Enteritis	*Aug 1925	Aug 1930
		Jan 1928	Ischiorectal abscess that drained		
		Mar 1928	Enteritis		
	2	Feb 1927	*Psoas abscess		*Apr 1927
	3	On admission (Dec 1926)	Draining tuberculous spine	Dec 1926	*Oct 1927
		Sept 1927	*Abscess closed, aspirated and opened		
	4	June 1930	Hemorrhage		*Aug 1930
		July 1930	*Left phrenemphraxis, pneumothorax		
	5	May 1930	*Enteritis		*Aug 1930
	6	On read mission (May 1928)	Draining empyema	May 1928	July 1928
	7	On admission (Oct 1930)	*Empyema	*Nov 1930	Jan 1931
	8	Aug 1930	*Enteritis		*Sept 1930
	9	Oct 1928	*Enteritis	*Oct 1928	*Feb 1929
		Dec 1928	*Enteritis (second attack)		
	10	Nov 1929	Hemorrhage		*May 1930
		Feb 1930	First stage thoracoplasty		
		Mar 1930	Second stage thoracoplasty		
		May 1930	*Third stage thoracoplasty		
	11	Mar 1930	Pleural effusion, left	*July 1930	*Dec 1931
		June 1930	*Purulent pleural effusion, right		
		Dec 1931	*High fever, extension of tuberculosis		
	12	Mar 1927	*Enteritis		*Mar 1927
	13	Dec 1927	*Pneumothorax		*Feb 1928
		Jan 1928	*Fluid, base of left lung		
	14	Oct 1921	Exercise prohibited	Apr 1918	*Dec 1921
		Nov 1921	*Flare up of tuberculosis		
	15	On admission (July 1923)	Psoas abscess	Apr 1925	Mar 1928
		Dec 1924	Pott's disease		
	16	Sept 1929	*Extension of tuberculosis	*Sept 1929	Dec 1931
		Jan 1930	Bad teeth, pyorrhea		
		May 1931	Questionable enteritis, slight obstruction		
	17	Jan 1930	Enteritis continuous to death	Mar 1933	(Terminal) Apr 1934
		Feb 1932	Exacerbation of enteritis		
		Aug 1932	Empyema		
	18	Sept 1927	Operation on ischiorectal abscess		Sept 1928
		Apr 1928	Furunculosis		
		May 1928	Rise of temperature		
		July 1928	*Spread of pulmonary tuberculosis		
		(Early 1926)	Enteritis began continuous throughout		
	19	Apr 1929	Examination of nasal ulcer		
		Nov 1933	Enteritis	Apr 1934	
	20	Apr 1932	Nausea and diarrhea, gradual progressive pulmonary tuberculosis with toxemia	Mar 1933	June 1933
	21	Dec 1926	Draining sinus, right lower quadrant, post operative (appendectomy)		*Dec 1927
		Aug 1927	Still draining		
		Dec 1927	*Empyema		
2	22	July 1924	Definite symptoms of enteritis, draining sinuses	July 1925	Nov 1925
		Feb 1925	Alternating constipation and diarrhea		
		July 1925	Enteritis		
	23	Jan 1932	Multiple sinuses draining	*May 1932	*Aug 1932
		Apr 1932	*High temperature		
		Aug 1932	*Sinus closed in right thigh		
	24	Oct 1930	Several draining sinuses	May 1932	Sept 1932
		Sept 1931	Abscess aspirated		
		May 1932	Heavy drainage from back		
		Aug 1932	Abdomen distended		
		Sept 1932	Liver enlarged		
	25	Mar 1930	Pleural fluid		Feb 1932
		June 1930	Empyema		
		July 1930	Enteritis (roentgen study)		
		Jan 1930	Granulations on vocal cords		

\* The items so marked are the most important clinical events and dates

TABLE 2—*Clinical Events and Onset of Renal Amyloidosis—Continued*

Group Case	Date	Clinical Event	Date of Presumptive Onset of Amyloidosis	Date of Definite Onset of Amyloidosis
2 (cont)	26 Apr 1928	First symptoms of enteritis	Oct 1928	
	June 1928	Lamp treatment for enteritis		
27	Nov 1928	*First symptoms of enteritis		*Nov 1928
	Dec 1928	Abdominal pain, diet for enteritis		
28	Mar 1929	Enteritis		Apr 1929
29	Dec 1931	Progressive tuberculosis	Mar 1932	
	Mar 1932	Liver palpable, tuberculous laryngitis		
30	Oct 1930	*Rectal fistula, tuberculous laryngitis	*Oct 1930	Mar 1931
31	1925	Insidious gastrointestinal symptoms ending in peritonitis and enteritis		May 1928
32	Feb 1929	Enteritis	June 1929	
33	Mar 1930	Enteritis		Oct 1931
34	May 1926	Symptoms of enteritis	July 1933	
	Feb 1927	No roentgen evidence of enteritis		
	Feb 1933	Diarrhea		
	July 1933	Enteritis, tuberculous laryngitis		
35	Mar 1934	*Cramps, *diarrhea, edema of ankles		*Apr 1934
	Apr 1934	*Enteritis, tuberculous laryngitis (liver and spleen not palpable)		
36	Sept 1924	Tuberculous laryngitis	Apr 1928	
37	July 1929	Serotal abscess (probably not significant)		Nov 1929
	Dec 1929	Diarrhea		
38	Feb 1927	Progressively weaker		*Jan 1928
	Nov 1927	*Diagnosis of cervical Pott's disease		
	Aug 1928	Draining sinus of neck		
39	Dec 1930	Psoas abscess draining	Nov 1931	
40	Aug 1920	Nephrectomy, sinus probably closed		Oct 1922
	Jan 1922	Opiates given, history suggests mild gastrointestinal disturbance		
	Mar 1923	Enteritis		
41	Oct 1926	Gastrointestinal symptoms began	*Apr 1927	Dec 1927
	Nov 1926	Pneumonic process		
	Feb 1927	Treatment suggests *enteritis		
42	Mar 1925	Gastrointestinal symptoms		
	Apr 1925	Enteritis		
43	Jan 1928	*Tuberculous laryngitis	*Feb 1928	*July 1928
	Feb 1928	*Increased activity of pulmonary tuberculosis with probable secondary infection		
	June 1928	*Enteritis		
	July 1928	Gastrointestinal distress		
	Aug 1928	Edema of ankles		
44	Oct 1926	Perineal abscess		June 1925
45		Nothing to account for original slight albuminuria (syphilitic treatment with heavy metals)		Aug 1927
	1927	Nothing to account for increase in albuminuria		
46	Mar 1929	Psoas abscess started	*Jan 1932	
	Dec 1932	*Rectal abscess		
47	Mar 1933	Encapsulated pleural fluid		
48	May 1926	Abdominal pain		
	Sept 1926	Appendectomy (tuberculous appendix)		
	Apr 1927	Abdominal distress		
	Oct 1927	Nausea, pain in side (complicating earci noma found at autopsy)		
49	Feb 1929	Isehiorectal abscess, stormy postoperative course, with healing later		
	Nov 1928	Enteritis		
50	July 1929	Symptoms of enteritis		
	May 1930	Apparently large liver		
51	Mar 1931	Diarrhea		
	Apr 1931	Enteritis		
	Aug 1931	Severe diarrhea		
52	Apr 1931	Gastrointestinal distress		
53	Feb 1933	Symptoms and roentgen diagnosis of enteritis		
54	Oct 1923	Multiple thromboses		
55	Mar 1929	Gastrointestinal distress		
56	Mar 1930	Anorexia		
57				

\* The items so marked are the most important clinical events and dates

of albuminuria was twenty-five months, the median being fifteen months (table 3) Thirty-nine patients had heavy albuminuria (2 plus and over) for an average of fifteen and four-fifths months, the median being six months The incidence of albuminuria and of heavy albuminuria was 82 and 68 per cent, respectively

TABLE 3—Data on Albuminuria

Case	Total Duration of Albuminuria, Months	Duration of Heavy Albuminuria, Months	Comments
<b>Group 1</b>			
1	63	2	Albuminuria preceded cylindruria by 30 months
2	12	12	
3	21	3	Albuminuria preceded cylindruria by 9 months
4	12	12	Variable in amount, absent on one occasion
5	16	13	Albuminuria preceded cylindruria by 4 months
6	2 (?)	3 (?)	Tuberculous empyema developed 10 months prior to readmission, which was probably onset of renal complication
7	17	16	Albuminuria preceded cylindruria by 2 months
8	4	4	
9	33	6	Albuminuria preceded cylindruria by 5 months
10	4	4	
11	5	1	Cylindruria preceded albuminuria by 17 months
12	44	44	
13	11	9	
14	171	131	Cylindruria preceded albuminuria by 5 months
15	96	62	Albuminuria preceded cylindruria by 34 months
16	15	15	Cylindruria preceded albuminuria by 25 months
17	22	2	Cylindruria preceded albuminuria by 33 months
18	67	67	
19	8	2	Albumin disappeared 5 months before death
20	21	18	
21	15	15	
<b>Group 2</b>			
22	52	7	Few casts
23	1	1	Cylindruria preceded albuminuria by 3 months
24	0	0	Cylindruria 5 months before death
25	34	2	Albuminuria preceded cylindruria by 3 months
26	3	3	No casts
27	2	2	
28	24	5	Albuminuria preceded cylindruria by 19 months
29	8	6	No casts
30	8	0	
31	1	1	Cylindruria preceded albuminuria by 6 months
32	1	0	
33	1	1	
34	1	0	
35	1	1	
36	13	0	
37	1	1	
38	21	18	
39	7	1	No casts
40	102	63	Cylindruria accompanied heavy albuminuria for first 20 months
41	15	9	Casts in last month only
42	36	0	Faint trace of albumin three times, no casts
43	9	7	Albuminuria preceded cylindruria by 2 months
44	41	35	Albuminuria preceded cylindruria by 3 months
45	48	13	Albuminuria preceded cylindruria by 35 months
46	30	0	Albuminuria preceded cylindruria by 3 months
47	0	0	No albumin or casts
48	36	0	Trace of albumin 4 times, no casts
49	18	0	Trace of albumin once no casts
50	0	0	No albumin or casts
51	0	0	No albumin or casts
52	0	0	No albumin or casts
53	0	0	No albumin or casts
54	0	0	No albumin or casts
55	0	0	No albumin or casts
56	0	0	No albumin or casts
57	0	0	No albumin or casts
Average	25 4	15 8	
Median	15	6	

## CYLINDRURIA

Fifteen patients showed no cylindruria, 11 only light cylindruria and 31 heavy cylindruria (table 4). The average total duration of the cylindruria in 42 cases was twenty-one and one-half months, the median

TABLE 4—Data on Urinary Sediment

Case	Duration of Light Cylindruria (Few to 1+), Months	Duration of Heavy Cylindruria (2 to 4+), Months	Variety of Cast		Leuko cytes	Erythro- cytes
			Hyaline	Granular		
Group 1						
1	30	2	+++	±	14+	0
2	12	7	++	+	±	0
3	12	12	++	+	±	0
4	12	12	++	±	1+	0
5	13	11	+++	+	±	0
6	1	1	++++	0	14+	0
7	15	15	0	+++	4+	+
8	4	4	++++	0	±	0
9	28	9	+++	±	±	0
10	4	1	+	+	±	Once*
11	22	21	+++	±	±	Once†
12	44	39	+++	±	±	0
13	11	11	++++	++	±	0
14	176	168	++++	++	2+	+
15	62	42	++++	±	3+	+
16	40	36	+++	±	1+	+
17	17	1	+++	+	+	+
18	67	63	++++	+	±	+
19	5	3	++++	+	+++	+
20	21	18	++++	+	+	+
21	15	6	++	±	+	0
Group 2						
22	51	0	+	±	+++	Once*
23	4	1	+++	±	+	0
24	5	0	+	±	±	0
25	32	2	+++	±	++	±
26	0	0	0	0	+++	0
27	2	2	++	+	++	0
28	5	0	+	+	+	0
29	0	0	0	0	++	0
30	8	3	++++	+	+	0
31	6	>1	++++	0	+	0
32	1	0	0	+	+	0
33	1	>1	++++	+	±	0
34	>1	0	0	±	+	0
35	1	1	+++	+++	±	±
36	1	0	+	0	+	0
37	1	0	+	±	+	0
38	21	0	+	0	++++	0
39	0	0	0	0	++++	++
40	63	63	++++	++	+	+
41	1	0	++	+	++	Once*
42	0	0	0	0	++++	0
43	7	7 (once)	+++	0	+++	+
44	38	38	++++	+++	++++	0
45	13	0	+	0	++++	0
46	30	0	+	0	±	0
47	0	0	0	0	±	0
48	0	0	0	0	+	0
49	0	0	0	0	±	±
50	0	0	0	0	±	0
51	0	0	0	0	±	0
52	0	0	0	0	±	0
53	0	0	0	0	+	0
54	0	0	0	0	+	0
55	0	0	0	0	+	0
56	0	0	0	0	±	+
57	0	0	0	0	±	+
Average	21.5	19.3				
Median	12	7				

\* Three months before death

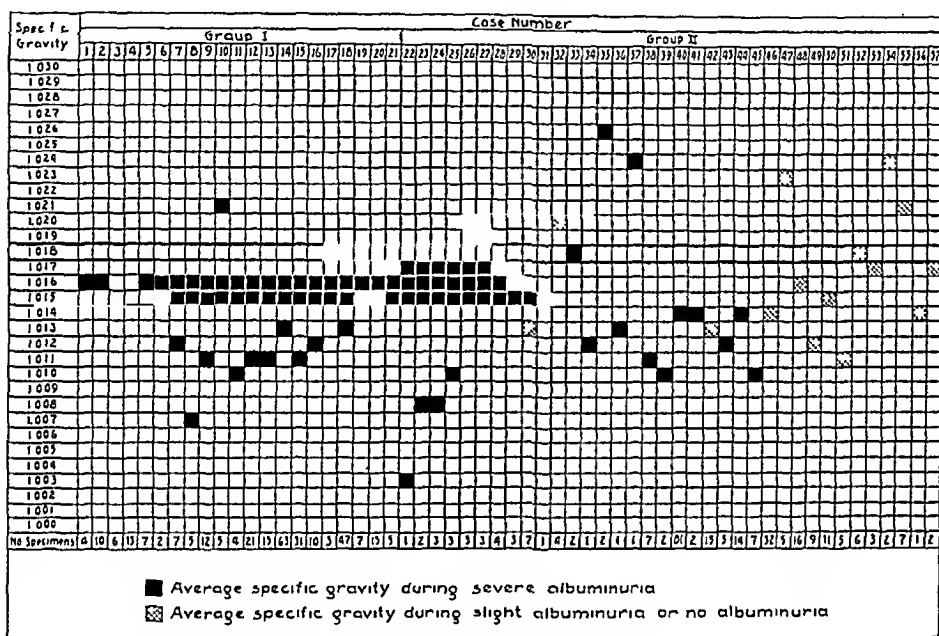
† Terminal

being twelve months. The average total duration of heavy cylindruria in 31 cases was nineteen and three-tenths months, the median being seven months.

Albuminuria appeared first in 12 cases, and cylindruria preceded albuminuria in 6. Six patients with albuminuria showed no casts, 3 of them having heavy albuminuria.

#### SPECIFIC GRAVITY

As explained in the preceding publication, we arrived at the figure 1.018 as the normal specific gravity for night urine of patients under sanatorium conditions. We also stated that the most constant and



The average specific gravity of the urine in individual cases

outstanding finding in renal amyloidosis was the low specific gravity of the urine. Only 1 of the 16 patients previously reported on retained the ability to secrete urine that had a normal or above normal specific gravity. In the added cases, even though the clinical features were not as outstanding and albuminuria was frequently absent, a low specific gravity was present in 30 of the 41 patients, or 73 per cent. A low specific gravity was present in 45, or 79 per cent, of the entire series of patients (see the accompanying chart).

#### FUNCTION OF THE KIDNEYS

Twelve patients were examined by means of the Volhard secretion and concentration test, as shown in table 5. Three showed a normal four hour output (80 per cent or above). Six showed normal dilution

TABLE 5—Results of Renal Function Tests

Case	Volhard Test			Output of Phenolsulfon phthalein in 2 Hours and 10 Minutes		Nonprotein Test for Nitrogen	
	Total 4 Hour Output, %	Maximum Dilution	Maximum Concen- tration <sup>*</sup>	Percentage	Time Before Death	Mg per 100 Cc	Time Before Death
Group 1							
1						33	1 mo
2	52	1 002	1 014	79 0	2 mo	24 35 24	2 mo 1½ mo ½ mo
3							
4						28	9 mo
5						31	½ mo
6				45 0	1 wk	33	1 wk
7				40 0	14 mo	34 31	14 mo 9 mo
8	50	1 002	1 012	47 5	2½ mo	27	1½ mo
9						29	3 mo
10						43	5 yr
11				40 0	9 mo	31	16 mo
12						39 160 174	2 yr 4 days 1 day
13	50 95	1 004 1 007	1 012 1 014	57 5 37 5	8 mo 5 mo	29 36 46	8 mo 2 mo 1 mo
14	64 49	1 002 1 003	1 021 1 017	45 0 40 0	4½ yr 2 yr 10 mo	33 34 33 60 50	6 yr 10 mo 4 yr 2 yr 10 mo 10 mo 7 mo
15	72	1 005	1 010	22 0	3 yr	41 72	39 mo 10 days
16	42	1 005	1 022	45 0	34 mo	32	34 mo
17	88	1 001	1 028	59 0	16 mo	23	16 mo
18	82	1 001	1 018	50 0 75 0	48 mo 12 mo	33 46	48 mo 12 mo
19				58 0 77 0	13 mo 7 mo	31	13 mo
20	59	1 000	1 027	85 0	10 mo	30	13 mo
21	71	1 003	1 024	55 0	5 mo	28	5 mo
Group 2							
22				42 0 62 0	39 mo 25 mo	41	8 mo
25				67 0	21 mo	34 27	21 mo 1 mo
26				55 0	2 mo	28	1 mo
28				66 0	8 mo	36	8 mo
38	15	1 005	1 012	22 0	16 mo		
39						34	6 mo
40				24 0 0 0	52 mo 2 mo 2 mo	27† 76 126	55 mo 2 mo 4 days
41				60 0	15 mo	33	15 mo
43						27	7 mo
44	27	1 011	1 014	27 0	6 mo		
45						115	1 day
48				65 0	17 mo		
Normal	80-100	1 001-1 002	1 028-1 032	55-70		30-35	

\* Concentrations of from 1 020 to 1 026 indicate moderate impairment, those from 1 010 to 1 020, marked impairment

† The urea nitrogen content of the blood was 13.6 mg per hundred cubic centimeters



(1 002 or below), and only 1 had normal concentration (1 028 or above) Five showed a marked reduction in initial output (50 per cent or less)

Twenty-four patients were given the standard two hour and ten minute intramuscular phenolsulfonphthalein test, and 12 of these had a normal output (55 per cent or above) In case 18 the test was repeated three years after the initial examination, and the output had dropped from 50 to 75 per cent Seven patients showed a moderate impairment of dye excretion (20 to 40 per cent output), and only 2 showed marked impairment (cases 18 and 40, with 75 and 0 per cent, respectively)

Of 29 patients for whom the nonprotein nitrogen content of the blood was determined, 5 showed a significant degree of nitrogen retention (50 mg or more per hundred cubic centimeters), 4 showed slight retention (40 to 50 mg) and 20 showed readings that were normal (below 40 mg) However, in 13 instances the determination was made more than three months before death, so it is possible that some of these patients had terminal nitrogen retention

#### BLOOD PRESSURE

As shown in table 6, for 47 patients the blood pressure was determined on entry Six of these patients (cases 13, 16, 24, 29, 31 and 47) showed a systolic reading of 130 mm or above In case 17 the blood pressure was elevated after entry and forty months before death Hypotension was a frequent finding However, low blood pressure readings are common among our patients at the sanatorium For 28 patients, one to several determinations of the blood pressure were made after the onset of presumptive or definite renal amyloidosis In 10 of these patients (cases 11 to 16, 18, 29, 44 and 47) there was elevation of the blood pressure (a systolic pressure of 130 mm or above), and 5 of them (cases 12 to 16) showed arteriolosclerosis of the kidney One patient (case 31) who had an elevated blood pressure on entry showed renal arteriolosclerosis Seven patients (cases 19, 25, 27, 33, 36, 38 and 42) showed some degree of renal arteriolosclerosis with a normal or low blood pressure, but for 5 patients (cases 25, 33, 36, 38 and 42) the blood pressure determinations were obtained one year or more before death One patient (case 45) had renal arteriolosclerosis, but no determination of the blood pressure was made One patient (case 12) showed a moderate grade of hypertension while under observation for renal amyloidosis He had marked nitrogen retention At postmortem examination the kidneys showed arteriolosclerosis and chronic nephritis In case 13 the condition may be termed latent hyper-

TABLE 6--Data on Blood Pressure

	Case	Date of Death	Admission		During Residence		Final Reading		
			Date	Blood Pressure, Mm of Mercury	Date	Blood Pressure, Mm of Mercury	Date	Blood Pressure, Mm of Mercury	Time Before Death
Group 1	1	9/ 3/30	12/ 5/24	100/66			Aug 1930	104/ 70	1 mo
	2	4/ 2/28	7/ 2/25		7/ 9/27	100/ 60	3/29/28	70/ 50	4 days
					3/19/28	104/ 90			
	3	9/11/28	12/31/26	104/64			July 1928	100/ 66	2 mo
	4	7/ 8/31	12/ 8/29	108/72	Sept 1930	102/ 62	10/30/30	90/ 70	9 mo
	5	8/ 4/31	8/13/26	108/48			11/ 7/30	104/ 64	9 mo
			6/ 7/29	106/50					
	6	7/27/28	5/18/28	125/78			7/26/28	100/ 60	1 day
	7	3/10/32	10/22/30	95/70			3/28/31	102/ 68	11½ mo
	8	1/17/31	8/21/29	102/66	10/18/30	102/ 74	11/13/30	108/ 80	2 mo
	9	5/ 1/31	6/ 4/28	110/85			1/24/31	108/ 65	3 mo
	10	8/29/30	2/27/18		4/23/24	110/ 80	5/15/30	118/ 80	3 mo
	11	4/ 9/32	11/21/29	120/72	9/ 6/30	138/100	11/13/30	116/ 92	16 mo
	12	10/10/30	8/30/24	118/74	10/18/28	136/ 80	4/10/30	174/ 92	6 mo
					7/19/29	142/ 82			
	13	12/26/28	12/26/25	148/90	1/ 1/26	125/ 90	11/22/28	135/ 94	1 mo
	14	10/12/32	4/10/17		1/ 3/22	130/ 80	5/29/32	194/120	5 mo
					12/29/25	140/ 98			
					10/18/28	228/122			
	15	3/24/33	7/25/23	108/80	1/ 1/26	125/ 67	3/ 9/33	108/ 62	½ mo
			12/12/24	106/75	10/10/28	120/ 78			
					2/ 4/30	150/ 90			
					12/ 6/32	136/ 74			
	16	12/ 4/32	7/20/29	140/88	2/ 4/30	162/110	11/24/32	178/120	½ mo
	17	7/ 1/34	3/25/29	112/82			3/31/31	136/104	40 mo
	18	3/18/34	2/17/26	102/66	4/ 7/30	102/ 70	2/ 2/33	132/ 94	13 mo
	19	8/14/34	7/ 1/31	104/72			4/19/34	108/ 70	4 mo
	20	12/20/34	5/29/27	110/70			11/ 1/34	104/ 76	1 mo
	21	3/ 7/29	4/13/27		Aug 1928	112/ 80			8 mo
Group 2	22	11/17/29	1/16/23	98/64					7 yr
	23	9/26/32	1/28/32	112/65					8 mo
	24	11/ 2/32	10/15/30	134/92					2 yr
	25	4/ 2/32	10/26/28	110/80					5½ yr
	26	1/ 7/29	11/ 2/27	100/20					1 yr
	27	1/11/29	11/ 6/28	92/60					2 mo
	28	9/ 2/29	9/ 6/27	92/64					2 yr
	29	11/24/32	11/25/27	140/92			3/18/32	148/ 86	8 mo
	30	6/ 9/31	10/22/30	116/80					8 mo
	31	5/29/28	11/23/27	136/82					6 mo
	32	7/ 2/29	10/ 3/28						
	33	11/24/31	6/29/29	124/80					29 mo
	34	7/27/33	4/ 5/24		5/ 1/28	135/ 95	7/13/33	90/ 76	14 days
	35	5/ 4/34	4/25/34	98/66					9 days
	36	5/12/28	9/11/24		1/16/26	88/ 48			2 yr
	37	12/30/29	1/12/29	116/74					11 mo
	38	6/11/29	6/24/18		8/ 6/27	100/ 48	6/19/28	104/ 52	12 mo
	39	12/22/31	5/ 2/31	122/78					7 mo
	40	12/20/27	6/10/19		11/20/27	90/ 62	12/17/27	68/ 38	3 days
	41	1/17/28	10/10/26						
	42	6/24/28	7/12/24	115/65					4 yr
	43	9/26/28	1/29/28	90/72					8 mo
	44	8/26/28	10/30/24		12/29/25	148/100			2½ yr
	45	9/28/28	6/20/22						
	46	6/22/34	12/10/27	120/88					6½ yr
	47	2/21/34	3/ 9/33	155/90					11 mo
	48	4/17/29	1/18/26	124/92					3 yr
	49	8/26/29	9/ 2/27	102/68					2 yr
	50	7/12/30	6/18/28	102/70					2 yr
	51	9/14/31	11/19/30	110/80					10 mo
	52	1/ 2/32	10/25/30	110/72					1 yr
	53	3/17/33	9/ 7/32	118/78					6 mo
	54	12/28/28	9/ 6/28	92/65					3 mo
	55	8/24/29	2/ 7/28	108/70					1½ yr
	56	7/13/30	7/ 9/30	92/46					4 days
	57	1/29/32	11/24/31	118/74					2 mo

tension Renal amyloidosis did not appear to influence his blood pressure He showed a slight elevation of the nonprotein nitrogen level one month before death At postmortem examination the glomerular lesion of chronic nephritis was present In case 14 there was marked and prolonged hypertension, the first evidence of which occurred four years after the onset of renal amyloidosis Because of the high blood pressure and the good renal function as regards the elimination of nitrogen during the period from eight to three years before death, we considered it highly probable that this patient had two conditions—renal amyloidosis and primary arterial hypertension At postmortem examination, marked arteriosclerosis and arteriolosclerosis and chronic nephritis were present In case 15 there was a slight degree of hypertension after the onset of renal amyloidosis The blood pressure became subnormal two weeks before death Postmortem examination showed arteriolosclerosis and chronic nephritis In case 16 there was a slight elevation of the blood pressure on entry Moderate hypertension developed At postmortem examination arteriosclerosis and chronic nephritis were present In cases 11, 17, 18, 29, 44 and 47 there were minimal increases in the blood pressure at some time during residence, without evidence of arteriolosclerosis, but in case 44 there was marked arteriosclerosis of the larger renal arteries

Of the 13 patients showing an elevated blood pressure at some time during residence, 12 were men, aged 21, 32, 33, 39, 45, 46, 53, 56, 57, 57, 58 and 72 years, respectively, and 1 was a woman, aged 26 years

One patient (case 40) was noteworthy in that he had had one kidney removed He showed marked albuminuria and cylindruria, with the phenolsulfonphthalein excretion diminishing to zero and with marked retention of nitrogen His blood pressure was low one month and also three days before death The eyegrounds showed no evidence of arteriolosclerosis or retinitis at the time of the last two determinations of the blood pressure This patient is cited as one who had an ample basis for "albuminuric retinitis" if the kidney alone were able to produce it independent of degenerative vascular changes in the retina This patient's condition in some respects was comparable to that in Anderson's<sup>2</sup> experimental animals Anderson removed about three fourths of the total renal tissue from rabbits and thereby produced a marked degree of nitrogen retention without causing either hypertension or retinitis

From the evidence presented it appears that hypertension occupies an inconspicuous position in the clinical picture of renal amyloidosis It may be incidental rather than related to cause and effect

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2 Anderson, H C The Relation of Blood Pressure to the Amount of Renal Tissue, *J Exper Med* 39 707 (May) 1924

## EXAMINATION OF EYEGROUNDS

In 19 cases an examination of the eyegrounds was made. In 11 (cases 1, 2, 4 to 9, 18, 19 and 40) the disks and retinas were normal, and there were no detectable vascular changes. In case 3 there was slight variation in the lumen of one inferior temporal artery. In case 13 one inferior temporal artery had a burnished appearance, suggesting an early "copper wire artery." In case 15 the arteries showed slight narrowing, and the choroid vessels were slightly prominent. The "pepper and salt" fundus was present in both macular regions. In case 17 one temporal artery had a burnished appearance, suggesting a "copper wire artery." In these 4 patients the vascular changes were so slight that they must be considered questionable. In case 11 the arteries showed slight dulling of the light reflex, with slight narrowing and irregularity of the lumen. We consider these changes indicative of early retinal arteriosclerosis. In case 12 there were a slight increase in the vascularity of the disks, marked tortuosity of vessels, an increased light reflex (early "copper wire artery") and moderate arteriovenous compression. In case 16 there were a moderately increased light reflex and irregularity of the lumen of the arteries, with slight arteriovenous compression. We consider that these 2 patients showed moderate retinal arteriosclerosis. In case 14 the arteries showed marked irregularity and narrowing of the lumen. Some were almost obliterated. There was slight compression at several arteriovenous crossings. This patient had marked retinal arteriosclerosis. All the patients examined were free from retinal hemorrhages and retinitis. It appears from this that the eyegrounds are usually normal in uncomplicated renal amyloidosis.

## PHYSICAL FINDINGS

Twenty patients had a special physical examination, which was usually made within one to three months after the onset of renal amyloidosis. The findings are shown in table 7. In the case of other patients not examined by us we are utilizing the bedside notes of the attending physician in establishing the presence of edema and enlargement of the liver. Slight to moderate pallor was noted in 13 patients. Slight to marked clinical edema was noted in 14 patients. In 8 it was slight, and in the remaining 6 it was of moderate to marked degree. In half the patients it was apparent only in the feet and legs. Edema, as noted at postmortem examination, was general in 10 instances. In 7 of these it was of slight to moderate degree. Localized edema, usually in the feet alone or in the hands and feet, was present in 31 cases, and in all but 2 cases it was of slight to moderate degree. Simon<sup>3</sup> found edema in 14 of 45 patients, and initial edema was present

3 Simon, S. Zur Klinik der Nephrose bei Knochen- und Gelenktuberkulose, *Deutsches Arch f klin Med* 163: 87, 1929.

TABLE 7—Physical Findings and Postmortem Weights

Case	Sex	Age at Death, Yr	Pallor	Edema		Periph eral Arterio sclerosis	Liver		Spleen		Heart Post mortem Weight, Gm	Physical Exam ination, Months Before Death
				Grade	Location		Cm Below Costal Margin	Post mortem Weight, Gm	Cm Below Costal Margin	Post mortem Weight, Gm		
Group 1												
1	F	33	2+	1+	Ankles, legs	3+	Enlarged	1,560	Enlarged	270	230	2
2	M	26	2+	3+	Legs, abdomen	1+	Not palpable	2,015	Not palpable	214	212	1
3	M	33	2+	0		0	3 0	3,405	0	475	210	4
4	F	25	0	0		0	0	2,666	0	340	146	12
5	M	28	2+	0		2+	8 0	3,070	0	246	163	10
6	F	23	1+	0		0	5 0	3,950	2	524	405	1
7	F	20	2+	2+	Face	3+	3 5	2,440	2	650	155	13
8	F	27	1+	0		0	3	2,730	0	245	160	3
9	F	42	2+	0		0	8	2,835	0	300	197	6
10	M	35						1,450		206	417	20
11	M	33	0	0		3+	0	2,325	0	263	223	7
12	M	56	0	0		2+	0	1,907	0	108	533	7
13	M	45	0	0		3+	0	1,200	0	240	297	2
14	M	53	2+	2+ 3+	Face, legs	3+	0	1,902	0	215	457	6
15	M	58	2+	1+	Legs	2+	0	2,800	4	543	335	42
16	M	72	0	0		2+	0	2,085	2	260	530	34
17	M	39	2		Ankles	2+		1,400	3	330	243	16
18	M	32	0			2+	4 5	3,017	0	331	315	13
19	F	33	3		Feet, ankles, leg, hand	2+	Not palpable	1,520	Not palpable	180	160	4
20	F	29	3	0	Ankles	2+	6 0	2,648	Not palpable	176	281	1
21	M	30						1,654		300		
Group 2												
22	M	39			Ankles, hand			2,430		345	360	
23	F	19						1,275		225	95	
24	M	21						1,885		485	109	

25	F	43	General	1,560	210	185
26	F	19	Ankles	1,805	179	174
27	M	68		1,210	240	270
28	F	29	Ankles	1,500	175	140
29	F	26	Ankles, wrists	1,534	250	175
30	F	28		1,375	170	175
31	M	46	Ankles	2,360	345	354
32	M	27	Feet	2,185	265	225
33	M	16		1,587	205	212
34	F	35		2,410	317	213
35	M	39	Ankles, hand	1,570	140	240
36	F	62	Ankles	1,115	208	300
37	M	24	Legs	1,870	280	210
38	F	11	General	1,030	194	216
39	M	32		1,155	165	147
40	M	36				
41	F	12		1,965	115	310
42	M	54				
43	F	28	Ankles	1,335	176	176
44	M	57		1,710	150	322
45	F	17		1,210	193	
46	M	33	Feet, hands, ankles	3,290	120	210
47	M	57		2,370	605	350
48	M	61	Feet, ankles	1,815	171	270
49	F	20	Ankles	1,850	115	125
50	M	29	Hands, ankles	2,806	215	252
51	F	22	Ankles	1,911	322	165
52	M	14	Ankles	1,460	200	210
53	F	32	Feet, ankles	1,340	299	198
54	F	18	Ankles	1,026	185	175
55	M	36	Ankles	1,300	60	250
56	M	71		1,165	202	295
57	M	23		1,525	363	332
Average				1,926 1	266 7	
Average in previous series of cases				2,337 5	320 7	

in 6 of 30 patients observed from the beginning. He stated that in a large number of patients no edema except terminal edema was present. Holten<sup>4</sup> stated that initial edema, as seen in ordinary nephritis, is not present. In 13 of his 30 patients there was no edema, and in only 3 was edema present that was not terminal. Our observations that the initial edema of ordinary nephritis is not present in renal amyloidosis agrees with Holten's observations. When edema is present in the early stage, its onset is more insidious. It will be approximately correct to say that one fourth of the patients with renal amyloid have edema at some time during the early and middle periods of the disease, while two thirds have terminal edema. One of our patients (case 12) had marked albuminuria for four years and at postmortem examination showed only slight generalized edema. Another patient (case 13) had severe albuminuria for nine months and no edema. We do not find any agreement in the amount of albuminuria and edema in our series. The condition is probably due to other factors than depletion of plasma protein by loss of albumin.

The clinical estimates of the enlargement of the liver and spleen together with postmortem weights are given in table 7. In 11 cases in which an examination was made less than six months before death, the examiner's estimate of the size of the liver and spleen was approximately correct when compared with the postmortem data. We assume that a 25 per cent increase in the size of the liver and an 80 per cent increase in the size of the spleen are necessary before enlargement of these organs can be demonstrated by physical diagnostic methods. These figures correspond closely with the standards of Barron and Litman,<sup>5</sup> who stated that a liver weighing 2,200 Gm or more and a spleen weighing 300 Gm or more are enlarged sufficiently to be demonstrable by palpation. These approximate the figures we used, namely, 2,250 Gm and 1,875 Gm, respectively, for the weight of the liver and 270 Gm for the weight of the spleen in either sex. We used as a basis for calculation 1,800 Gm as the normal weight of the liver in men and 1,500 Gm as the normal weight in women and 150 Gm as the normal weight of the spleen in either men or women. These figures closely approximate the normal figures given by Boyd.<sup>6</sup> In 13 of 31 men the weight of the liver was not increased (1,800 Gm or less). In 2 cases the postmortem examination was not made at the sanatorium, and we are not using the weights reported. In 9 of 24 women the weight of the liver was not increased (1,500 Gm or less).

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4 Holten, C. Nephritis Caused by Tuberculosis, *Acta med Scandinav* **61** 107, 1924.

5 Barron, M., and Litman, A. B. Importance of Hepatomegaly and Splenomegaly in Differential Diagnosis, *Arch Int Med* **50** 240 (Aug) 1932.

6 Boyd, E. Normal Variability in Weight of the Adult Human Liver and Spleen, *Arch Path* **16** 350 (Sept) 1933.

On the basis of the postmortem weight there was enlargement of the liver in 60 per cent of the cases. If it is assumed that the weight of the liver must increase 25 per cent before enlargement can be demonstrated by physical examination (2,250 Gm in men and 1,875 Gm in women), in only 10 men and 9 women were these levels reached (34.5 per cent). If enlargement of the liver that was demonstrable by physical examination had been made a diagnostic requirement in this series, the diagnostic error would have been 65.5 per cent.

In 4 of 31 men and in 2 of 24 women the weight of the spleen (150 Gm) was not increased. The incidence of enlargement of the spleen on the basis of the postmortem weight was 89 per cent. If it is assumed that an 80 per cent increase in the size of the organ is necessary before enlargement can be demonstrated by physical examination, it is found that enlargement was present in 28 cases, or 59 per cent. Thus, if demonstrable enlargement of the spleen had been made a diagnostic requirement, the diagnostic error would have been 41 per cent. If the usual textbook diagnostic triad of chronic suppuration, enlargement of the liver and spleen and albuminuria had been insisted on, the diagnostic error would have been 89 per cent. Cases 3, 6, 7, 9, 22 and 31 are the only ones in which these requirements were met.

The congo red test, according to the technic of Bennhold,<sup>7</sup> was performed on 7 patients (cases 6, 8, 9, 11, 14, 15 and 18). The percentage of disappearance of the dye was 100, 40, 39, 90, 90, 100 and 100, respectively. In cases 8 and 11, with a disappearance of 40 and 39 per cent, respectively (in the doubtful range), there was enlargement of both liver and spleen, while in case 14, with 90 per cent disappearance, there was only slight enlargement of the liver and spleen. While the congo red test is helpful in the diagnosis of amyloidosis, our experience in this series of cases and in others leads us to believe that there is too great variability of response to make it a dependable diagnostic test on which to base an early diagnosis.<sup>8</sup> We performed the test only in

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7 Bennhold, H. Ueber die Ausscheidung intravenös eingegebenen Kongorotes bei den verschiedensten Erkrankungen insbesondere bei Amyloidosis, *Deutsches Arch f klin Med* **143** 32, 1923.

8 Since the preparation of this manuscript there has been published by S. Lipstein an evaluation of the congo red test for amyloidosis (*Am J M Sc* **195**: 205, 1938), in which he has made the following statement: "The congo red test can be interpreted only as confirmatory evidence of amyloid disease when the percentage of dye absorption is 90 per cent or higher." In the absence of amyloidosis in 91 tuberculous patients, he found the dye absorption to be from 10 to 75 per cent in all instances, with 4 exceptions in which values of 80, 90, 95, and 100 per cent, respectively, were recorded. In 34 cases of amyloidosis observed at postmortem examination, the absorption values were from 90 to 100 per cent in all but 5 cases, the exceptions being values of 82, 60, 35, 35 and 35 per cent.



TABLE 8—*Diagnostic Scheme* \*

Case	Point 1			Point 2		Point 3		Point 4		Post mortem Renal Amyl	Contrary Urinary Findings	Comment																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																	
	Suppurating Focus	Clinical Enteritis	Tuberculous Membrane	Albuminuria	Cylindruria	Enlarged Liver	Enlarged Spleen	Specific Gravity of 1.015 or Below	Diagnosis																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																				

27	0	+	0	+	+	0	0	0	0	2	A	+	0	Amyloid kidney should have been diagnosed because of combination of enteritis and heavy albuminuria
28	0	+	0	+	+	0	0	0	0	2	A	0	0	Amyloid kidney should have been diagnosed because of combination of enteritis and heavy albuminuria
29	0	0	0	+	+	0	0	0	0	1	A	+	0	Only reason for suspecting amyloid kidney, increasing albuminuria in last 5 months of life
30	0	0	0	+	+	0	0	+	+	2	A	0	0	Amyloid kidney should have been suspected from urinary findings
31	+	+	+	+	+	+	+	+	+	4	A	0	0	Amyloid kidney should have been diagnosed, missed because albuminuria appeared late
32	0	+	0	+	+	0	0	0	0	2	A	0	0	Meager urinary findings until terminal stage, amyloid kidney might have been suspected because of enteritis and albuminuria
33	0	+	0	+	+	0	0	0	0	2	A	0	0	Terminal evidence only, but amyloid kidney should have been suspected because of enteritis and heavy albuminuria
34	0	+	0	+	+	+	+	+	+	4	A	0	0	Meager urinary findings and terminal only, but diagnosis should have been made or at least strongly suspected because of enteritis, enlarged liver and spleen
35	0	+	0	+	+	0	0	0	0	2	A	0	0	Terminal evidence only, but amyloid kidney should have been diagnosed because of enteritis and heavy albuminuria
36	0	0	0	+	+	0	0	+	+	2	A	0	+	Meager urinary findings only, no reason for suspecting amyloidosis
37	0	0	0	+	+	0	0	+	0	2	A	0	0	Heavy terminal albuminuria only, careful physical examination might have demonstrated enlargement of spleen
38	+	0	0	+	+	0	0	0	0	3	A	+	0	Should have been diagnosed amyloid kidney, poor follow up study
39	+	0	0	+	+	0	0	0	0	3	A	+	+	Amyloid kidney should have been suspected, missed because of absence of casts and presence of pyuria
40	0	0	0	+	+	0	0	+	+	2	A	+	+	Only one kidney, diagnosis missed because chronic nephritis without hypertension was suspected
41	0	0	0	+	+	+	0	+	0	3	A	+	0	Diagnosis missed because of inexperience, no casts (except during last month) and pyuria influenced diagnosis
42	0	+	0	0	0	0	0	+	+	2	A	+	0	Only faint trace of albumin, marked pyuria, little grounds for suspicion
43	0	0	0	+	+	0	0	0	0	2	A	+	+	Should have been suspected, unduly influenced because of absence of casts and presence of pyuria and hematuria
44	0	0	0	+	+	0	0	0	0	2	A	+	0	Should have been suspected, influenced by pyuria and few casts, one of first cases studied
45	0	0	0	+	+	0	0	0	0	2	A	+	0	Should have been diagnosed because of long continued heavy albuminuria and cylindruria
46	+	0	0	0	0	+	+	+	+	3	A	0	0	Should have been strongly suspected or even diagnosed
47	+	+	+	0	0	0	0	0	0	2	A	0	0	Probably should have been diagnosed amyloidosis of liver and spleen
48	0	0	0	0	0	0	0	0	0	1	A	0	0	No basis for suspicion
49	0	+	0	0	0	0	0	0	+	1	A	0	0	Enteritis with low specific gravity of urine should have raised suspicion
50	+	+	+	0	0	+	0	0	0	2	A	0	0	Amyloid disease should have been suspected
51	0	+	0	0	0	0	+	+	+	3	A	0	0	Amyloid kidney should have been suspected without albuminuria
52	0	+	0	0	0	0	0	0	0	1	A	0	0	No basis for suspicion
53	0	+	0	0	0	0	+	0	0	2	A	0	0	Amyloid disease should have been suspected
54	0	0	0	0	0	0	0	0	0	0	A	0	0	No basis for suspicion
55	0	0	0	0	0	0	0	0	0	0	A	0	0	No basis for suspicion
56	0	0	0	0	0	0	0	0	0	1	A	0	0	Low specific gravity of urine was only reason for suspicion
57	0	0	0	0	0	0	0	+	+	1	A	0	+	Enlarged spleen was only basis for suspicion

\* Slight albuminuria and slight cylindruria were not assigned a point value

cases in which the diagnosis had been made. We admit, however, that in doubtful cases a positive reaction to the congo red test should carry considerable weight. We are now employing this test and obtaining plasma protein determinations in all cases of suspected renal amyloidosis, and we hope to define the usefulness of these procedures in the early diagnosis of amyloid kidney.

#### COMMENTS ON DIAGNOSIS

We have evolved table 8 on a basis of the clinical findings, and we believe that its use will lead to the discovery of a larger number of cases of amyloid kidney in sanatoriums for patients with tuberculosis. This table is constructed on the basis of a four point diagnosis. From the standpoint of importance we group the suppurating focus, enteritis and tuberculosis of the serous membranes together, if any one of these conditions is present, this counts one point in the diagnosis. Albuminuria accompanied by or in the absence of cylindruria counts a second point. While in no case did cylindruria run its whole course without albuminuria, there are times when cylindruria should be assigned a value in the absence of albuminuria, especially if there is the more or less characteristic sediment with the "one type" hyaline cast with fat droplets, as mentioned in a former publication. In this tabulation we have not designated that albumin was present in the urine unless it occurred with more or less constancy and in significant amount. We have eliminated cases in which there was an occasional or faint trace of albumin or a similar degree of cylindruria, such as conceivably might occur in any patient seriously ill with tuberculosis. Third in importance is enlargement of the liver and spleen. Our criteria for enlargement have previously been mentioned. We employ direct and indirect percussion as well as palpation. The normal extent of dulness of the liver should be approximately 7 and 10 cm. at the midline and at the mammary line respectively, and if these figures are increased by 2 cm., the liver should be considered enlarged. By the same method, the long diameter of the spleen in the normal person is 10.5 cm., and when it is 12.5 cm. or above, it should be considered enlarged.

The normal specific gravity of the night urine under sanatorium conditions in 200 nonfatal and 80 fatal cases in which there was no renal disease was found to average 1.018. We are taking 1.015 or below as a significant departure from normal. We do not consider that this finding is as important in establishing the diagnosis as the first three that have been mentioned, but it occurs with sufficient frequency (61 per cent) so that it should be given some consideration. Renal function tests of water secretion and concentration and of the

output of dye, determinations of the nonprotein nitrogen content and of the blood pressure, and eyeground examinations have their place in the differential diagnosis of amyloidosis from the other nephropathies. Edema likewise is usually absent when a case comes up for diagnosis.

Referring to table 1, it will be seen that 41 patients (72 per cent) had a suppurating focus, clinical enteritis or tuberculosis of serous membranes or these conditions in combination and that 33 patients also had albuminuria and cylindruria. Both enteritis and albuminuria occurred 25 times (44 per cent), the most frequent association. Enlargement of the liver or spleen or both occurred 28 times (51 per cent).

In reviewing the diagnostic table it is seen that 29 patients (51 per cent) had either a three or four point diagnosis, which we feel was sufficient for a clinical diagnosis of renal amyloidosis. If the patients with a suppurating focus or clinical enteritis who later showed albuminuria are added, the number is increased to 37 (65 per cent), we believe that this is a safe diagnostic practice. It must be taken into account, however, that all these patients had tuberculosis.

#### PATHOLOGIC EXAMINATION

Other body tissues, in addition to the kidney, were studied for the presence of amyloid. The tissues, in addition to gross examination after the iodine test, were also examined microscopically after hematoxylin and eosin and methyl violet stains had been employed. The distribution of the amyloid observed in the various organs is shown in table 9. In all cases amyloid was present in the kidney and spleen, but in 5 instances it could not be demonstrated in the liver. The adrenal glands, mesenteric lymph nodes, tracheal lymph nodes, small and large intestine, pancreas and thyroid contained amyloid, the amount decreasing in the order named. Our findings are in close accord with those of Rosenblatt.<sup>9</sup>

The weight of the kidneys and the microscopic distribution of amyloid are given in table 10. When the degree and duration of albuminuria and cylindruria are compared with the amount and distribution of amyloid in the kidney, it is possible to make some generalization. The patients with the greatest amount of amyloid in the glomeruli were usually those in whom the albuminuria was most marked and of the longest duration. All the patients with marked albuminuria at some time showed amyloid in the glomeruli, and only 6 of 42 patients with marked albuminuria had a slight amount. The patients with marked albuminuria usually showed a heavy deposit of amyloid also in the other parts of the kidney.

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<sup>9</sup> Rosenblatt, M. B. Amyloidosis and Amyloid Nephrosis, *Am J M Sc.* 86:558 (Oct.) 1933.

TABLE 9—*Distribution of Amyloid as Observed Post Mortem* \*

Case	Kidney	Liver	Spleen	Pancreas	Adrenals	Mesenteric Lymph Nodes	Retropertitoneal Lymph Nodes	Appendix	Tracheal Lymph Nodes	Thyroid	Small Intestine	Large Intestine
Group 1												
1	A	A	A	—	a	—	0	—	—	0	—	—
2	A	A	A	A	A	A	A	—	—	0	—	—
3	A	A	A	A	A	?	0	A	A	0	—	A
4	A	A	A	A	A	—	0	—	—	—	—	A
5	A	A	A	—	A	A	0	—	—	—	A	A
6	A	A	A	—	?	?	0	—	—	0	—	—
7	A	A	A	—	A	—	—	—	—	—	?	A
8	A	A	A	A	A	—	0	—	—	0	A	0
9	A	A	A	A	a	—	0	A	—	A	—	—
10	A	A	A	—	A	—	0	—	—	0	A	—
11	A	A	A	—	A	A	—	—	?	A	—	—
12	A	A	A	—	A	—	0	—	—	0	—	—
13	A	a	A	—	A	—	0	—	—	0	—	—
14	A	A	A	—	A	A	A	—	—	A	—	—
15	A	A	a	—	A	—	0	—	—	A	A†	—
16	A	A	A	—	A	—	0	—	—	?	—	—
17	A	—	A	—	A	—	0	—	A	?	—	—
18	A	A	A	a	A	—	0	—	—	0	A	A
19	?	—	A	—	—	—	0	—	A	—	—	—
20	A	A	A	—	A	a	0	—	—	—	—	—
21	A†	A	A	—	A	0	0	Op	0	0	0	0
Group 2												
22	A	A	A	—	A	0	0	0	—	0	0	0
23	A	A	A	A	A	A	A	A	A	—	A	—
24	A	A	A	—	A	A	A	A	—	—	—	—
25	A	A	A	—	A	—	0	—	—	—	—	—
26	A	A	A	—	A	A	0	0	A	0	A	A
27	A	a	A	—	0	—	0	0	—	0	—	0
28	A	A	A	—	—	0	0	0	0	0	0	—
29	A	A	A	?	A	—	—	—	—	—	—	—
30	A	A	A	—	a	—	0	Op	—	—	—	—
31	A	A	A	—	A	—	0	—	A	0	—	—
32	A	A	A	—	A	—	0	—	0	0	0	0
33	A	A	A	—	a	A	0	—	A	—	A	A
34	A	A	A	a	A	0	0	A	A	a	—	A
35	A	A	A	—	A	—	0	0	—	a	—	—
36	A	A	A	—	A	A	0	A	A	0	—	A
37	A	—	A	—	?	A	0	—	0	0	0	0
38	a	—	A	—	—	0	0	0	—	0	0	0
39	A	—	A	—	—	a	0	a	—	0	a	a
40	A	A	A	a	A	—	0	Op	a	0	a	a
41	A	A	A	A	A	A	0	Op	A	0	A	A
42	A	A	A	—	—	—	0	—	A	0	—	—
43	A	A	A	—	a	—	0	—	—	0	0	—
44	A	A	a	—	A	a	0	—	a	0	—	—
45	A	A	A	A	A	a	0	—	—	0	—	—
46	A	A	A	—	A	A	0	Op	—	—	—	a
47	A	A	A	—	a	A	0	—	—	—	—	—
48	A	A	A	—	A	—	0	Op	—	0	0	—
49	A	A	A	—	A	0	0	—	?	0	—	—
50	A	A	A	—	A	—	0	—	—	0	—	—
51	A	A	A	—	A	A	0	A	A	—	A	A
52	A	—	A	—	A	—	0	—	A	—	—	—
53	A	a	A	—	A	—	0	Op	?	A	—	—
54	a	—	a	—	—	—	0	—	—	0	0	—
55	a	—	A	—	—	?	0	0	0	0	—	—
56	a	—	a	—	—	a	0	—	—	0	—	—
57	a	—	A	—	—	A	0	—	A	0	A	—
Number examined	57	57	57	57	55	51	7	43	52	23	48	50
Number with amyloid	57	47	57	10	46	20	4	8	17	8	14	11

\* A indicates amyloid found, a, small amount of amyloid, —, no amyloid, 0, tissue not examined (none saved), Op, operative removal, ?, doubtful amyloid

† Gross examination only

‡ Pylorus

TABLE 10—*Distribution of Amyloid and Other Lesions in the Kidney*

Group 1	Case	Weight of Kidney, Gm	Amount of Amyloid				Thickened Bowman's Capsule	Tubules		Sclerosis		Infiltration
			Cortex		Medulla			Suppression, with Dilata- tion of Those Remaining	Epithelial Degeneration	Arteries	Arterioles	
			Glomeruli	Interstitial	Capillaries	Interstitial						
	1	234	±	—	—	+	—	—	+	—	—	—
	2	515	++	+	+	±	—	—	+	—	—	—
	3	213	+	+	++	±	—	+	—	—	—	—
	4	268	++	±	+	±	—	—	+	—	—	—
	5	242	++	±	+	+	—	—	+	—	—	+
	6	427	++	+	+	—	—	++	+	—	—	+
	7	848*	±	+	—	++	—	++	—	—	—	+
	8	309	++	±	+	++	—	—	++	—	—	—
	9	315	++++	+	++	+++	+	++	—	—	—	+
	10	271	±	±	±	—	—	—	+	—	—	—
	11	326	++	+	+	++++	—	+	+	—	—	—
	12	276	+++	±	++	+++	++++	++	+	+	+	+
	13	330	+	+	+	—	+++	++	+	++	++	+
	14	415	++++	+	+++	+	+	++	+	++	++	+
	15	286	++++	++	+++	+++	++++	+++	+	++	++	+
	16	433	++++	+	+++	++	+	++	+	++	+	+
	17	512	++	—	+	+	—	+++	++	—	—	—
	18	181	++++	++	++	—	++	++	—	—	—	+
	19	270	±	—	—	±	—	—	+	—	+	—
	20	314	+++	—	+	++	—	—	—	—	—	±
	21	369										
Group 2												
	22	719	++++	+	++	+	++	+	++	—	—	+
	23	238	+++	+	++	++	—	—	—	—	—	—
	24	187	++	+++	++	++	+	++	+	+	—	—
	25	210	++	++	+	+	++	++	+	+	±	+
	26	340	+++	+	++	++	—	+	+	—	—	±
	27	795	++	+	+	++	+	+	+	—	+	+
	28	225	++	—	++	++	—	—	—	—	—	+
	29	455	+++	+	++	—	—	+	++	—	—	—
	30	200	+	—	+	+	—	+	+	—	—	+
	31	351	++	+	+	++	—	—	+	+	+	+
	32	332	+	—	+	+++	—	—	—	—	—	—
	33	253	+++	—	++	++	±	+	+	±	±	+
	34		+++	+	++	+	—	—	+	±	±	—
	35	370	+	±	+	—	—	++	+	—	—	—
	36	164	++	—	+	++	+	—	+	—	+	—
	37	382	++	+	+	+	—	+	+	—	—	+
	38	202	±	+	—	+	+	++	+	++	+	±
	39	345	±	—	+	—	—	±	—	—	—	±
	40		++++	+++	++	+++	++	++	+	+++	+++	+++
	41	280	++++	+++	++	+++	++	+++	±	++	++	+
	42		+	++	±	++	—	+	+	±	—	±
	43	250	++	—	+	—	—	+	+	—	—	—
	44	255	++++	++	++++	+	++	+++	+	+++	—	±
	45	221	++++	+++	+++	+++	++	+++	+	++	+	+
	46	405	+	±	++	+	—	—	—	—	—	+
	47	415	±	—	±	+	—	—	—	—	—	—
	48	266	+	+	++	+++	±	—	—	—	—	—
	49	215	++	—	—	—	±	—	—	—	—	—
	50	319	+	—	+	+	—	—	+	+	±	—
	51	328	++	+	++	±	—	±	—	—	—	—
	52	350	+	—	+	—	—	±	—	—	—	—
	53	400	+	±	+	—	—	±	—	—	—	—
	54	240	±	±	±	±	—	—	—	—	—	—
	55	281	±	—	—	—	—	—	+	—	—	—
	56	342	—	—	—	—	—	—	—	—	—	—
	57	393	±	—	±	±	—	—	—	—	—	—
Average 410.9												

\* Enormous tuberculous abscess of right kidney

It may also be stated that a low specific gravity is usually associated with amyloid in the interstitial tissue of the renal cortex. Few patients who maintained a specific gravity of 1.016 or above showed amyloid in the interstitial tissue. Only 5 of 21 showed as much as 1 plus amyloid. However, 9 of 36 patients with a low specific gravity showed no amyloid in the interstitial tissue.

#### SUMMARY AND CONCLUSIONS

The clinical course in 57 cases of renal amyloidosis occurring in tuberculous patients in which amyloid deposits were demonstrated in microscopic section of renal tissue stained with methyl violet at post-mortem examination is presented.

Tuberculous enteritis was the clinical complication occurring most often in association with renal amyloidosis. If only pathologically verified cases are considered, the incidence of tuberculous enteritis was approximately 60 per cent. If amyloid infiltration of the intestine is added (which includes all cases in which there was a pathologic basis for the symptoms), the incidence was 70 per cent. If cases in which the diagnosis was not verified at necropsy are added, enteritis was present in 82 per cent. Thirty-six patients (65 per cent) showed tuberculous pleuritis, pericarditis or peritonitis alone or in combination.

A suppurating focus was present in 18 patients (exclusive of patients with pulmonary cavitation).

The date of the presumptive or definite onset (or both) could be determined with reasonable accuracy in 46 cases. An outstanding clinical event or complication that might be associated with the onset of renal amyloidosis occurred in 25 cases (54 per cent). Such clinical events, complications or conditions were the onset of enteritis, pleural effusion, empyema, the development of other suppurating foci, the institution of pneumothorax and other surgical procedures.

Ten patients showed no albuminuria. The average duration of albuminuria when present was twenty-five months, the median being fifteen months. The average duration of heavy albuminuria was fifteen and eight-tenths months, the median being six months. Albuminuria preceded cylindruria in 12 cases.

Fifteen patients showed no cylindruria. The average total duration of cylindruria when present was twenty-one and one-half months, the median being twelve months. The average total duration of heavy cylindruria was nineteen and three-tenths months, the median being seven months. Cylindruria preceded albuminuria in 6 instances.

Urine with a low specific gravity was the most constant manifestation of impaired renal function. It occurred in 4 of every 5 cases. It was an early finding and, contrasted with chronic nephritis, was not associated with nitrogen retention.

Impaired concentration was a frequent finding, as shown by the Volhard test performed in 12 cases. A diminished four hour output and impaired dilution occurred with decreasing frequency. The intramuscular phenolsulfonphthalein test gave normal results in 12 of 24 cases. Only 5 of 29 patients for whom nonprotein nitrogen determinations for the blood were obtained showed a nitrogen retention of 50 mg or more per hundred cubic centimeters.

Hypertension, according to our data, occupies an inconspicuous place in the clinical picture of renal amyloidosis. It may be incidental rather than related to cause and effect.

Arteriolosclerosis of the retinal vessels is present even less often than hypertension. Retinitis was not observed in 19 patients examined. The group examined were patients with outstanding clinical symptoms.

It is approximately correct to say that one fourth of the patients with renal amyloidosis have edema at some time during the early and middle periods of the disease, and two-thirds have terminal edema. There is no agreement between the loss of albumin via the kidney and the edema.

We have constructed a table in which the presumably causative factor, albuminuria, enlargement of the liver and spleen and the low specific gravity are each assigned a one point value with respect to the diagnosis. We believe that if this is used as a guide it will lead to the early discovery of a larger number of cases of renal amyloidosis in sanatoriums for patients with tuberculosis.

In general, the greater the number of diagnostic points, the greater the amount of amyloid present in the renal tissues.

In our cases if the old textbook triad of chronic suppuration, albuminuria and enlargement of the liver and spleen had been insisted on, the diagnostic accuracy would have been 11 per cent.



# ASPIRATION FOR REMOVAL OF BIOPSY MATERIAL FROM THE LIVER

REPORT OF THIRTY-FIVE CASES

EDGAR BARON, M D

NEW YORK

The clinical diagnosis and prognosis of hepatic disease are frequently beset with considerable uncertainty and inaccuracy, despite the aid of numerous tests of hepatic function and recent improvements in the technic of roentgen examination. As a result, patients with hepatomegaly are often subjected needlessly to exploratory laparotomy, the liver being found to be studded with metastatic carcinoma. On one recent occasion, diagnostic aspiration of the liver was performed in a case in which hepatic suppuration was suspected (case 1). Aspiration yielded a few fragments of tissue which on histologic examination showed carcinoma. This work was subsequently extended, and forty-seven additional aspirations of tissue for biopsy were performed in thirty-four cases. It was observed that, as a procedure for patients in the wards, the diagnosis of obscure hepatic disease often could be made by this method with a reasonable degree of safety. The danger of hemorrhage, which has deterred surgeons from removing specimens for study, even at operation, may be obviated if certain precautions are observed.

Hepatic aspiration is not a new procedure. As far back as 1833 Roberts<sup>1</sup> and Biëtt<sup>2</sup> reported its use in the treatment of hepatic suppuration and hydatid disease. It remained the treatment of choice in these two diseases until the advent of antiseptic surgery, when it gradually fell into the discard. With advances in histologic technic, it was revived as a diagnostic aid. Bingel,<sup>3</sup> in 1923, reported on 100 aspirations, with 2 deaths due to hemorrhage. Olivet,<sup>4</sup> in 1926, reported that

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From the medical service of Dr. George Baehr, the Mount Sinai Hospital.

1 Roberts. Abscess of the Liver, with Hydatids, Operation, *Lancet* **1** 189-190, 1833.

2 Biëtt. Hydatides du foie, avec développement considerable de cet organe, ponction explorative, incision, sortie d'une grande quantité d'acephalocystes, guérison, *Gaz d hôp* **7** 383, 1833.

3 Bingel, A. Ueber der Parenchypunction der Leber, *Verhandl d deutsch Gesellsch f inn Med* **35** 210-212, 1923.

4 Olivet, J. Die diagnostische Leberparenchypunction, *Med Klin* **22** 1440-1443, 1926.

he had performed one hundred and forty aspirations, with 3 deaths, 2 being due to hemorrhage and 1 to peritonitis. Huard<sup>5</sup> reported several cases and mentioned that he had outlined an abscess cavity with iodized poppyseed oil 40 per cent.

#### TECHNIC

The elective site of aspiration has been subject to considerable variation. Many observers recommend the intercostal approach, either in the nipple line,<sup>3</sup> the anterior axilla,<sup>6</sup> the midportion of the axilla<sup>7</sup> or posteriorly.<sup>3</sup> However, those who have recorded cases in which death was due to hemorrhage<sup>8</sup> have claimed that the intercostal approach is dangerous. They concluded that a tear in the parenchyma of the liver may occur as the organ descends with inspiration, since the needle may be fixed between two ribs. In all our early cases there was hepatomegaly, and aspiration could therefore be made below the costal margin. In the absence of hepatomegaly, aspiration can be done safely to the right of the epigastrium, immediately below the costal margin and in the general direction of the lower portion of the right axilla. Aspiration was performed at first intercostally, in several cases of jaundice, without untoward effects. However, in view of the potential danger, in all subsequent cases aspiration was performed below the costal margin.

As the procedure often causes a dull pain, despite the use of local anesthesia, it has been found advisable to reinforce the anesthesia with a liberal dose of a strong hypnotic. Paraldehyde, given orally in doses of from 8 to 30 cc about one hour prior to aspiration, has been found effective in the majority of cases.

The necessary equipment includes a 20 cc Luer-Loc or "record" syringe and a 13 gage needle, about 9 cm long. After the administration of a local anesthetic, the skin is punctured with a bistoury. The needle is directed upward and laterally and kept fairly superficial, thus avoiding important structures, such as large vessels or bowel. Once the parenchyma of the liver has been reached, constant suction is maintained in order to obtain a core of hepatic tissue. The specimen can be freed from blood if the contents of the syringe are poured through a double thickness of gauze. The pieces of hepatic tissue are then fixed in a solution of formaldehyde U S P (diluted 1:10), and the remainder of the specimen can be removed from the syringe by rinsing the instrument with solution of formaldehyde. The tissue is then sectioned in the routine manner for histologic study.

5 Huard, P., May, J. M., and Joyeux, B. La ponction biopsie du foie, *Ann d'anat path* **12** 1118-1124, 1935.

6 Sims, J. M. Treatment of Hepatic Abscess by Aspiration, *Tr M Soc Virginia* **3** 106-111, 1879.

7 Hammond, W. A. Some Points in the Pathology and Treatment of Hepatic Abscesses, *St Louis M & S J* **35** 72-76, 1878.

8 Bingel<sup>3</sup> Olivet<sup>4</sup>

## REPORT OF CASES

Although aspiration has been performed on patients with suppurative disease of the liver, these cases have not been included here, because it is felt that this is a recognized procedure and does not belong within the scope of the present paper.

The 8 following cases are presented in detail to illustrate the diseases in which hepatic aspiration is of greatest value. The first 2 cases are representative of the cases in which there was hepatomegaly, carcinoma being suspected clinically, the diagnosis was confirmed in both cases by hepatic aspiration. In the next 2 cases there was hepatomegaly, in 1 case due to congenital cystic disease and in the other to a large cavernous hemangioma. Histories are given of 3 cases in which there were different types of hepatogenous jaundice (catarrhal icterus, coarse nodular cirrhosis and obstructive jaundice) and of a case of proved cirrhosis of the liver.

**CASE 1**—C. G., a 46 year old man, had had mastectomy in the right side (presumably for carcinoma) about five years prior to his present illness. For the past two years he had received hypertonic saline solution intravenously for angina pectoris. On entry he complained of a sensation of distress in the right upper quadrant of the abdomen associated with flatulence of four weeks' duration. Immediately prior to his entry the pain became severe, and the possibility of acute cholecystitis or of acute hepatitis following therapy with saline solution was considered. On examination the entire upper portion of the abdomen was acutely tender and rigid. The temperature varied from 102 to 104 F. The leukocyte count was 20,000 and the sedimentation rate 18 mm in sixteen minutes. It was thought that he probably had suppurative cholecystitis, with perforation and spreading peritonitis. Operative intervention was deferred because of the patient's poor condition. After a few days the fever and leukocytosis subsided, and the pain disappeared. However, the liver had enlarged, extending about 10 cm. below the costal margin. In view of this finding, the possibility that carcinoma was compressing the hepatic vein was considered. About three days later the patient again had fever and leukocytosis, associated with copious expectoration of green, mucoid sputum and signs of consolidation of the upper lobe of the right lung. With the object of differentiating between metastatic carcinoma and hepatic suppuration, a specimen was aspirated from the liver. No pus was obtained, histologic examination of the aspirated tissue showed carcinoma. The patient died, and at postmortem examination primary carcinoma of the bronchus of the upper lobe of the right lung, with extensive metastasis to the liver, was present.

*Comment*—This case served to attract our attention to the diagnostic possibilities of hepatic aspiration, particularly in the diagnosis of metastatic carcinoma of the liver.

**CASE 5**—S. G., a 53 year old woman, complained of pain in the right lower portion of the chest, an increase in abdominal girth and loss of 8 pounds (3.6 Kg.) in the past three months. This was later accompanied by edema of the ankles. On examination she appeared thin and emaciated. A node the size of a cherry was felt in the left infraclavicular region. The right side of the diaphragm was high and did not move with respiration. The abdomen was distended and

doughy, and there were alternating areas of flatness and resonance, which did not shift with change in the patient's position. The liver extended about 10 cm below the costal margin. There were numerous tortuous veins extending from the inguinal region over the abdomen and chest. The current of blood was from below upward, suggesting obstruction of the inferior vena cava. The leukocyte count was 13,900 and the hemoglobin value 58 per cent. Roentgen examination of the chest showed that the right side of the diaphragm was high. A pyelogram, made after intravenous injection of a contrast medium, was unsatisfactory. The node in the left infraclavicular region was excised and showed the presence of neurofibroma. It was felt that hepatic aspiration afforded the best method of arriving at a diagnosis. A large quantity of caseous material was aspirated, this proved to be a specimen of malignant Grawitz tumor.

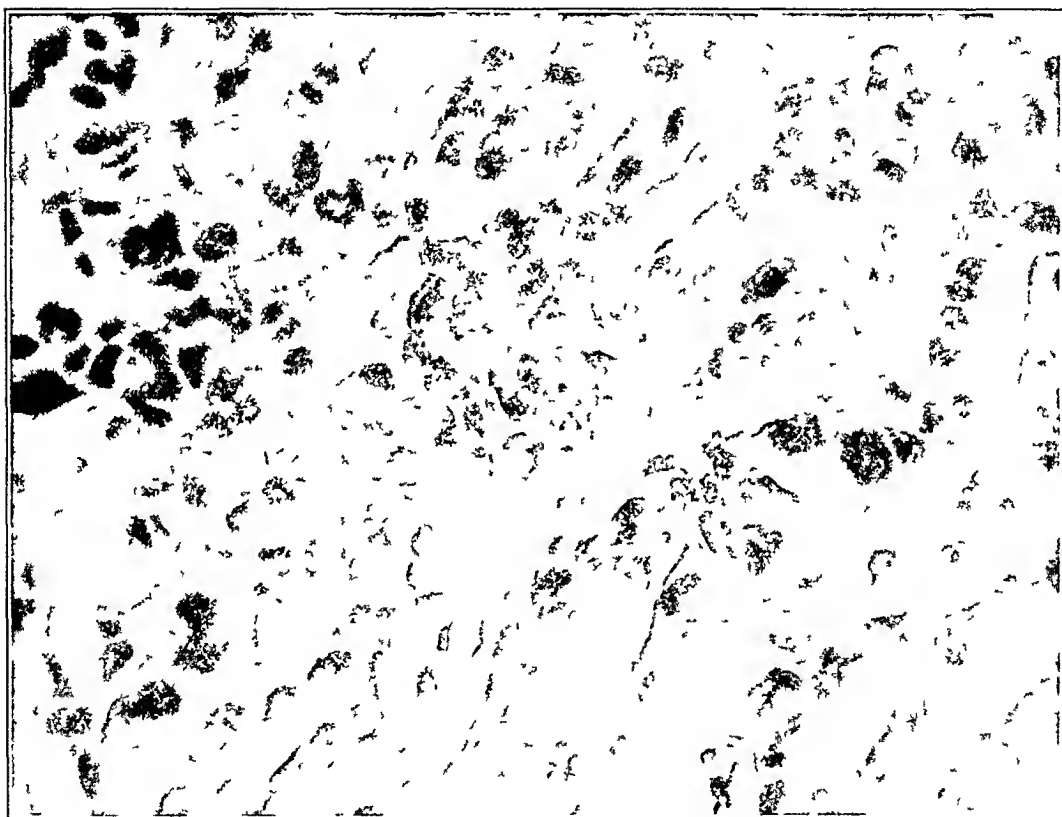


Fig 1 (case 3)—Adenocarcinoma

*Comment*—The reason for the collateral circulation now became clear. Apparently the tumor had invaded and obstructed the inferior vena cava. The loculated abdominal fluid was attributed to peritoneal invasion.

CASE 12—B E, a 53 year old man, had one episode of hematuria, nine years prior to admission to the hospital, which persisted for five days. He then showed progressive dyspnea on exertion. A mass developed in the upper portion of the abdomen and gradually increased in size during the past four years. On examination he appeared thin and chronically ill. The liver extended about 20 cm below the costal margin, the surface was firm and nodular, without tenderness. The spleen and the left kidney could be palpated. There was moderate edema of the ankles. The hemoglobin value was 90 per cent, the leukocyte count 17,000 and the sedimentation rate normal. The galactose tolerance test showed values within

normal limits Examination of stools showed no blood, ova or parasites A congo red test showed 28 per cent retention of dye in the tissues The value for total protein was reduced to 52 per cent (albumin, 31 per cent, globulin, 21 per cent) The value for urea nitrogen was 21 mg per hundred cubic centimeters of blood The icteric index was 1 The cholesterol content was 200 mg and the cholesterol ester content 65 mg per hundred cubic centimeters Several specimens of urine revealed a trace of albumin, occasional erythrocytes and clumped leukocytes A Rehfuess test meal showed a diminution in the content of free hydrochloric acid Roentgen examination of the chest, long bones and gastrointestinal tract revealed no abnormality Pneumoperitoneum showed the liver to be large, nodular and adherent to the under surface of the diaphragm The spleen was enlarged The reason for the hepatosplenomegaly was obscure Cardiac failure, amyloid disease or cirrhosis seemed unlikely In spite of the prolonged history, the possibility of carcinoma was strongly suspected by some observers Aspiration of a specimen from the liver was carried out at two different sites, and two different types of clear fluid were obtained, one yellow and the other colorless This limited the possible diagnoses to either echinococcosis or congenital cystic disease The fluid contained no scolices, the complement fixation test for echinococcosis gave negative results for both fluid and blood A pyelogram showed the presence of congenital cystic disease of the kidneys

*Comment*—In this case hepatic aspiration provided the first clue to the correct diagnosis, as the presence of congenital cystic disease of the liver and kidneys had not been suspected

CASE 15—P S, a 41 year old woman, since pregnancy seven years ago, had complained of severe epigastric pain which occurred one or two hours after meals and was relieved by self-induced vomiting or with sodium bicarbonate She attributed a loss of 52 pounds (23.6 Kg) to the fact that she was afraid to eat Ten months prior to entry her appendix was removed in an effort to alleviate the pain At that time a small cutaneous cavernous hemangioma was removed from the left temporal region

On examination the patient appeared thin and emaciated The left lobe of the liver extended about 10 cm below the costal margin, its surface was smooth and acutely tender The right lobe was barely palpable There were no significant laboratory findings Roentgen examination of the chest and abdomen and a pyelogram shed no light on the diagnosis Pneumoperitoneum showed a mass, the size of a grapefruit, merging with the shadow of the liver Examination of the gastrointestinal tract showed that the stomach was pushed to the left, the lesser curvature being compressed by an extrinsic mass The second portion of the duodenum was drawn toward the liver and fixed As all the diagnostic measures had failed to reveal the nature of the underlying disease, an attempt was made to aspirate material for biopsy The skin was anesthetized, but each time that an attempt was made to anesthetize the peritoneum, venous blood was aspirated Since the surface of the liver does not ordinarily contain large blood vessels, it was concluded that the hepatic enlargement could be explained by the presence of a large cavernous hemangioma The surmise was confirmed at operation, the hemangioma being merged with the left lobe of the liver As there was no line of cleavage, resection was impossible

*Comment*—Fortunately hepatic aspiration was not completed in this case, for the attempt to introduce a large needle into a hemangioma might possibly have resulted disastrously

CASE 19—G R, a 37 year old man, a Puerto Rican who had resided in the United States for thirty years, complained that two weeks prior to admission to the hospital he experienced nausea, vomiting and anorexia. One week later he had a dull epigastric pain, accompanied by jaundice, dark urine and clay-colored stools. There was no history of ingestion of drugs. On examination he appeared deeply jaundiced. The liver and spleen were both palpable. The stool was brown and showed a strongly positive reaction for urobilinogen. The urine showed a 3 plus reaction for bile and urobilinogen in a dilution of 1 to 20. The cholesterol content was 230 mg and the cholesterol ester content 96 mg per hundred cubic centimeters of blood. The icteric index was 38 (acetone extraction method). The bilirubin value was 10 mg per hundred cubic centimeters. The van den Bergh test showed a prompt positive reaction. The Wassermann reaction was

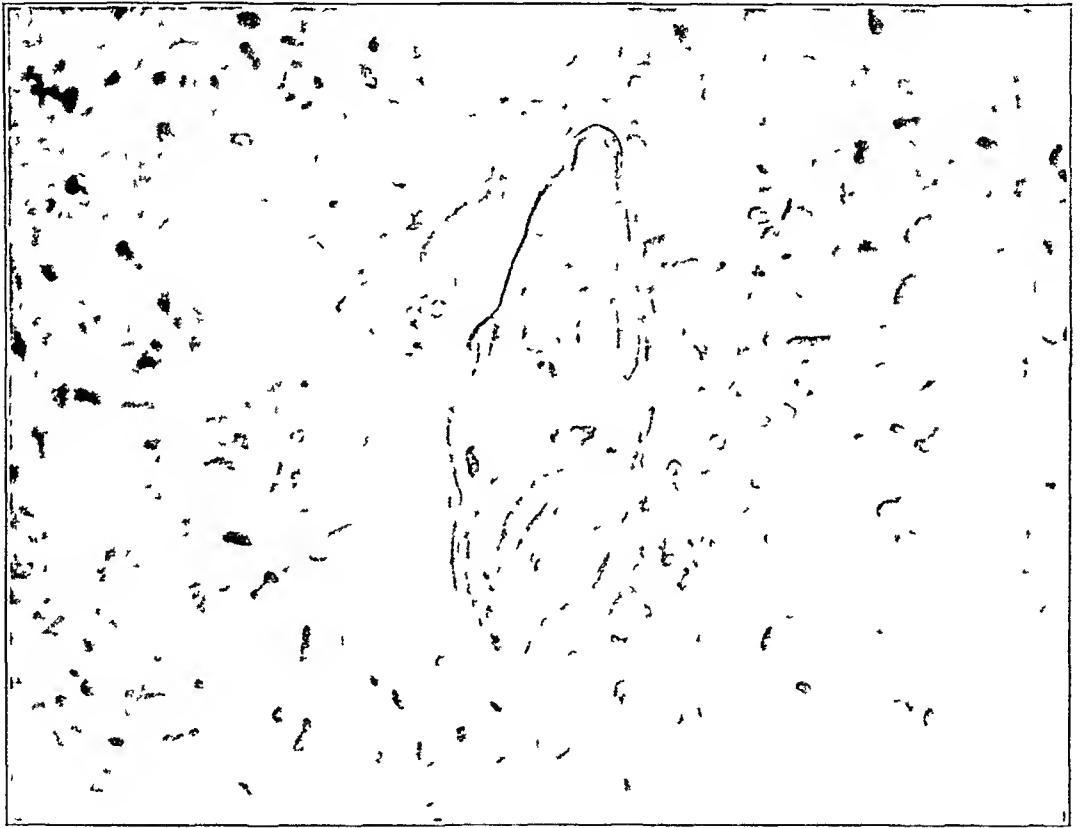


Fig 2 (case 19)—Tubercle-like reaction surrounding an ovum of *Schistosomum*

negative. A galactose tolerance test showed impaired hepatic function (9.49 Gm was excreted). A sodium benzoate test showed an excretion of less than 0.96 Gm.

The data indicated that this was probably a case of typical catarrhal jaundice in an early stage. It was felt that aspiration of biopsy material would be of value in determining the underlying pathologic condition and would also serve as a means of comparison with tissue obtained from patients with other types of jaundice. The specimens showed parenchymatous degeneration and inspissated bile in the bile capillaries. Aspiration was repeated several weeks later, after subsidence of the icterus. On this occasion there was no evidence of degeneration or icterus, although the icteric index had not yet returned to normal. Incidentally, a granuloma was discovered surrounding an ovum of *Schistosomum mansoni*. Examination of the stool subsequently revealed several ova. It seemed probable that the parasite had remained viable for at least thirty years.

CASE 23—L H, a 48 year old woman, eight weeks prior to admission to the hospital began to complain of anorexia, nausea and malaise. Several days later there appeared jaundice, which rapidly became intense. Although the stools were light at the onset, they soon resumed their normal color. Six weeks after the onset she experienced moderate pruritus. No history of biliary colic was elicited. On examination she appeared deeply icteric. The liver extended 10 cm below the costal margin. Throughout the period of observation specimens of urine contained abundant quantities of bile. Urobilinogen was present in dilutions varying from 1:5 to 1:160. The cholesterol content of the blood was 460 mg and the cholesterol ester content 110 mg per hundred cubic centimeters. The icteric index varied from 10 to 40 units. The bilirubin value was 3.5 mg. The van den Bergh test showed a prompt positive reaction. Culture of bile obtained by duodenal drainage revealed a bacillus of the diphtheroid group, *Streptococcus haemolyticus* (beta), *Staphylococcus albus* and *Bacillus welchii*. The gallbladder was not visualized by means of the Graham test, and no opaque stones were seen. The galactose test revealed an excretion of 8.11 Gm. The sodium benzoate test showed an excretion of less than 1.2 Gm.

In view of the long history of unremitting jaundice, exploratory operation seemed indicated. However, the hepatic function tests suggested severe primary degeneration of the liver. After eleven weeks of jaundice, hepatic aspiration was performed, the biopsy specimen showing chronic and acute interstitial hepatitis, parenchymatous degeneration and icterus. No inspissated bile was present in the bile capillaries. In view of these findings it appeared that the jaundice could be attributed either to coarse nodular cirrhosis following severe degeneration of the liver or cholangitis lenta. When seen five months after the onset, the patient was still icteric, with no signs of recovery.

CASE 25—R S, a 65 year old woman, had lost considerable weight during the past six months. She had complained of jaundice, pruritus, dark urine and tendency to bruise easily for four weeks prior to admission to the hospital. On examination she was moderately icteric. The liver extended about 10 cm below the costal margin, the edge was hard and irregular. The urine showed a 4 plus reaction for bile and urobilinogen in a dilution of 1 to 5. The sedimentation rate was 18 mm in seventeen minutes, the leukocyte count was 20,000. A specimen of stool contained a trace of urobilinogen. The cholesterol content of the blood was 340 mg per hundred cubic centimeters. The icteric index was 30. The value for bilirubin was 5 mg per hundred cubic centimeters. The van den Bergh test showed a prompt positive reaction. The galactose tolerance test gave values within normal limits, although the sodium benzoate test revealed an excretion of only 0.4 Gm. The clinical diagnosis in this case was obstructive jaundice, possibly due to carcinoma of the head of the pancreas. The hepatic aspiration, which showed inspissated bile in the bile capillaries and acute inflammation of the periportal fields, confirmed the impression of obstructive icterus. The patient refused cholecystogastrostomy as a palliative procedure.

CASE 32—J Y, a 52 year old woman, had had mild recurrent attacks of pain in the upper abdominal region during the past two years. The pain had become more severe during the past three months and was associated with a dragging sensation in the left upper quadrant. The liver extended 8 cm below the costal margin and felt firm. The spleen extended 10 cm below the costal margin. The leukocyte count was 1,800, with a normal differential count. The number of platelets was reduced to 90,000. The cholesterol content of the blood was 265 mg and the cholesterol ester content 30 mg per hundred cubic centimeters. The

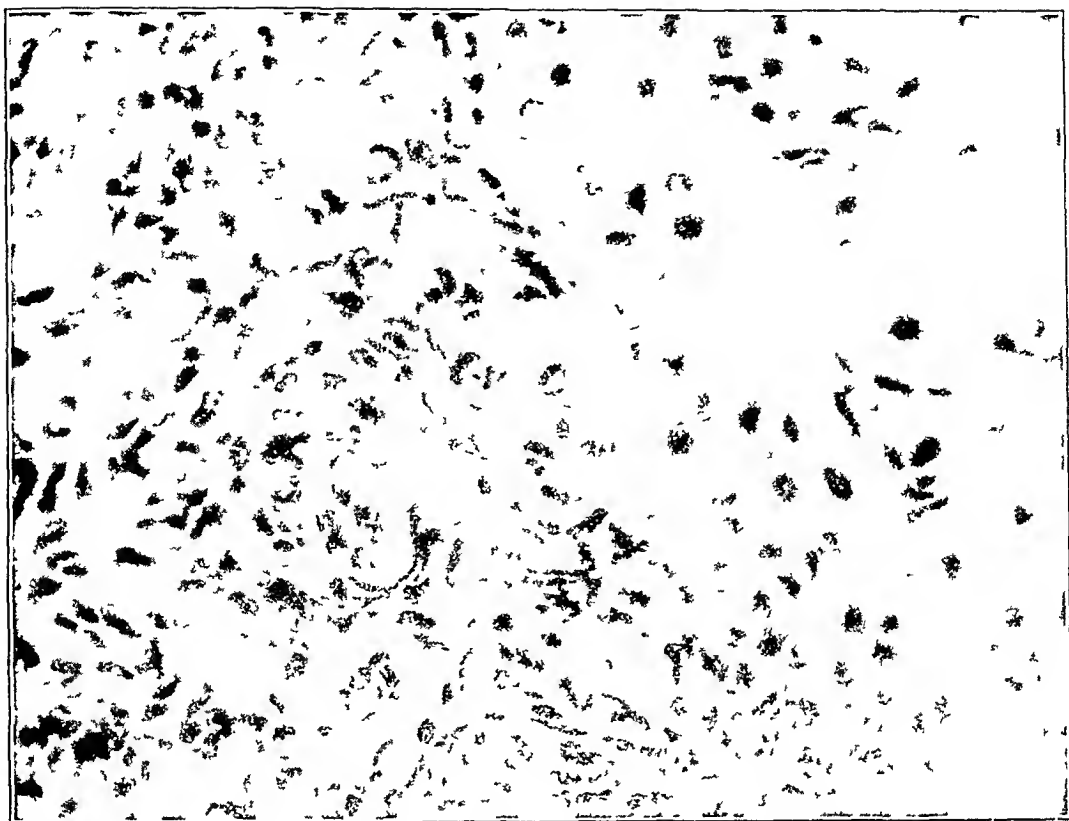


Fig 3 (case 23) —Hepatic degeneration with fibrosis

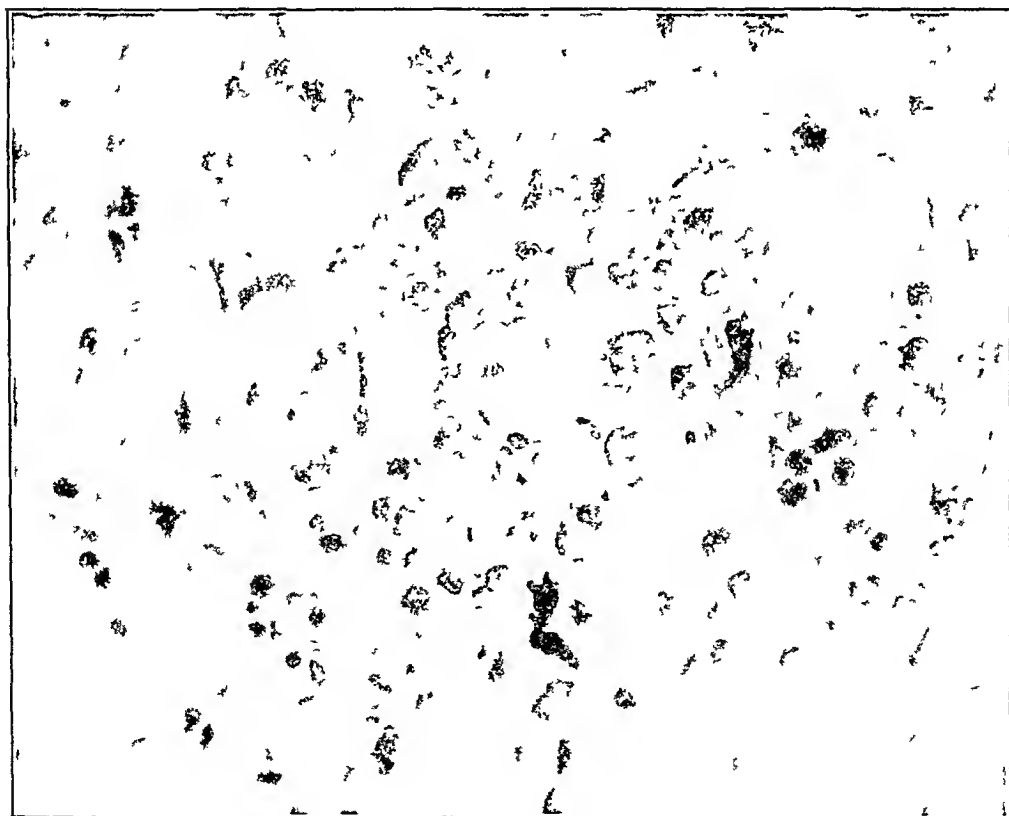


Fig 4 (case 25) —Thrombi in bile capillaries



Takata-Ara test of the blood serum gave a 2 plus reaction. Pneumoperitoneum showed hepatosplenomegaly. Sternal and splenic punctures revealed no abnormal findings. It was felt that the probable diagnosis was Laennec's cirrhosis, possibly with thrombosis of the splenic vein. Although the biopsy specimen obtained by hepatic aspiration showed an increase in fibrous tissue, this was not sufficiently characteristic to warrant the diagnosis of cirrhosis. Since the patient's symptoms appeared to be due to enlargement of the spleen, splenectomy was performed. The spleen was large and succulent and contained about 500 cc of blood. The liver presented the appearance typical in cases of Laennec's cirrhosis. The patient made an uneventful recovery. The platelet count rose to 750,000 and the leukocyte count to 8,800.

*Comment*—The data relative to the cases in which hepatic aspiration was performed are presented in the accompanying table, with the clinical impression prior to aspiration, the histologic details and the ultimate course.

#### COMPLICATIONS

While no serious complications were encountered in the group of cases reported in this paper, other observers have reported several types of untoward accidents. These may be classified under the following headings:

- 1 Hemorrhage
- 2 Infection

- (a) Introduced from the outside
- (b) After perforation of a hollow viscus
- (c) After entrance into an abscess cavity

Hemorrhage is the most common cause of death, according to the reports in the literature. Five instances in all have been reported, by Bingel,<sup>3</sup> Olivet,<sup>4</sup> and Toullec,<sup>9</sup> these occurred in cases in which aspiration was probably performed intercostally. The bleeding in these instances was attributed to the fact that the needle was held between two ribs, the liver being torn as it descended with inspiration. This complication can be eliminated by performing the aspiration below the costal margin, and the large vessels can be avoided if the needle is kept superficial.

When postmortem examination was performed in the cases reported in the present study, there was no evidence that bleeding had occurred. Usually the site of aspiration could not be identified, or was revealed by a minute area of organized thrombus. Minor bleeding probably does occur in some cases, as is shown by the fact that vomiting may take place immediately after the needle is withdrawn. A patient who is awake may complain of pain at the site and also of pain referred to the region of the right shoulder. Sometimes there is a slight rise in temperature,

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<sup>9</sup> Toullec, F., and Huard, P. La ponction exploratrice du foie, *Monde méd.*, Paris 45 990-999, 1935.

*Data Regarding Thirty-Five Cases*

Case No	Initials	Diagnosis	Pathologic Report on Tissue Aspirated	Comment
<b>Carcinoma</b>				
1	C G	Metastatic carcinoma or hepatic abscess	Carcinoma	Postmortem diagnosis primary carcinoma of bronchus of upper lobe of right lung, with hepatic metastases
2	F H	Metastatic carcinoma	Carcinoma	No operation
3	J K	Metastatic carcinoma	Adenocarcinoma	No operation
4	F F	Metastatic carcinoma	Anaplastic carcinoma	Postmortem diagnosis primary gastric carcinoma with hepatic metastases
5	S G	Metastatic carcinoma	Malignant Grawitz tumor	No operation
6	M T	Metastatic carcinoma, cirrhosis	1 Malignant growth, possibly sarcoma 2 Normal liver 3 Normal liver, colonic mucosa aspirated	Exploratory laparotomy was performed three days after last aspiration, no leak or peritoneal reaction, postmortem examination showed primary gastric carcinoma with hepatic metastases
7	L H	Metastatic carcinoma	Adenocarcinoma	No operation
8	S G	Metastatic carcinoma	1 Few tumor cells suggestive of carcinoma 2 Carcinoma 3 Carcinoma	No operation
9	L B	Metastatic carcinoma	1 No hepatic tissue 2 Lymphocytic focal infiltration, inflamed granulation tissue 3 Densely arranged spindle cells with occasional mitotic figures	Postmortem diagnosis primary bronchogenic carcinoma with hepatic metastases
10	E T	Metastatic carcinoma	Immature cell carcinoma (small cell type)	No operation
11	D M	Cirrhosis with ascites	Scirrhous carcinoma	No operation
12	B E	Metastatic carcinoma	No tissue was obtained, only clear, yellow fluid	Congenital cystic disease of liver and kidneys
13	H R	Metastatic carcinoma or abscess	Normal liver	No operation subsequent course slowly downhill, carcinoma probably present and not found
14	J R	Carcinoma of lung, ascites	Normal liver	Metastases probably present
15	P S	Metastatic carcinoma	Blood only	Cavernous hemangioma present at operation
16	M L	Metastatic carcinoma	Fatty liver	Resection of carcinoma of colon 10 years ago, probably no metastases
17	G K	Carcinoma of the stomach	Normal liver	At operation, primary gastric carcinoma, liver, free from metastases
18	D K	Hepatomegaly, amyloid disease or cirrhosis	1 Normal liver 2 Carcinoma	Diagnosis of carcinoma not suspected clinically until appearance of ascites
<b>Jaundice</b>				
19	G R	Catarrhal jaundice	1 Hepatic degeneration and icterus 2 Schistosomiasis	Probably two independent diseases, namely, catarrhal icterus and schistosomiasis, the latter subsequently recovered in stool
20	M E	Jaundice, multiple parasite infestation	Normal liver	<i>S. mansoni</i> , <i>Necator americanus</i> and <i>Trichurias</i> recovered from stool
21	O B	Catarrhal jaundice	Normal liver	Specimen removed at fourth week, when jaundice was receding
22	D S	Catarrhal jaundice	Slight periportal inflammation no hepatic degeneration	Specimen taken late in disease, uneventful recovery

*Data Regarding Thirty-Five Cases—Continued*

Case No	Initials	Diagnosis	Pathologic Report on Tissue Aspirated	Comment
<i>Jaundice—Continued</i>				
23	L H	Coarse nodular cirrhosis	1 Hepatic degeneration 2 Thickening of periportal fields and infiltration with polymorphonuclear leukocytes and lymphocytes	After five months, jaundice still present
24	J R	Coarse nodular cirrhosis	1 Fibrosis and infiltration with leukocytes 2 Bile casts	Jaundice persisted after five months
25	R S	Carcinoma of pancreas	Inspissated bile in bile capillaries	No operation
26	J E	Carcinoma of pancreas	Obstructive icterus and acute cholangiolitis	No operation
27	K H	Carcinoma of pancreas	Obstructive jaundice with cholangiolitis	At operation primary papillary adenocarcinoma of gallbladder, obstruction due to glandular metastases
28	L S	Hepatitis or carcinoma of pancreas	Obstructive jaundice, sub-acute cholangiolitis	Jaundice slowly receding, diagnosis not clear
29	J B	Carcinoma of pancreas	Chronic and acute periportal inflammation, obstructive icterus	At operation carcinoma of head of pancreas, with hepatic metastases
30	I N	Anemia, hepatomegaly, jaundice	1 Hemosiderosis and inflammation 2 Hemosiderosis and inspissated bile in bile capillaries 3 Hemosiderosis and periportal round cell infiltration	Aplastic anemia confirmed by bone marrow examination jaundice appeared after transfusion, liver became progressively larger, cause still obscure
<i>Miscellaneous</i>				
31	I W	Cirrhosis	Normal liver	No operation, clinical diagnosis clearly indicative of cirrhosis
32	J Y	Cirrhosis	Normal liver	At operation Laennec's cirrhosis with splenomegaly
33	N P	Cirrhosis	Periportal inflammation, no cirrhosis	No operation, final clinical diagnosis, cirrhosis
34	Y S	Cholecystitis	Normal liver	At operation stone in common bile duct without obstruction
35	D N	Diabetes mellitus	Normal liver	Hepatomegaly probably due to ptosis

which persists for forty-eight hours. These symptoms may be due to extravasation of blood in the peritoneal cavity. The vomiting and the pain in the shoulder, first noted by Dieulafoy,<sup>10</sup> in 1872, can be attributed to the presence of a small amount of blood on the under surface of the diaphragm, but otherwise these symptoms appear to be of little importance.

Local infection at the site of the puncture or peritonitis introduced from without can be attributed only to improper technic.

Olivet<sup>4</sup> reported a death due to peritonitis, which may have followed perforation of the bowel, resulting in an intestinal leak. In 1 of our first cases (case 6) a small piece of colonic mucosa was recovered, but there was no untoward reaction. When the patient was operated on, three days later, neither the site of aspiration in the liver nor the

<sup>10</sup> Dieulafoy, G. Kystes hydatiques, *Gaz d hôp* 45 586, 595, 603, 614, 621, 644, 691 and 780, 1872.

site of entry into the colon could be found. There was no intestinal leak or peritoneal reaction. The possibility of peritonitis after aspiration of a hydatid cyst or a hepatic abscess is remote, indeed, this was the method of choice for the treatment of these two conditions during the past century, and many authors stressed the point that peritonitis was not one of the complications encountered.

#### COMMENT

The cases in which hepatic aspiration was performed can be grouped according to the diagnostic problems presented.

- 1 Hepatomegaly without jaundice (18 cases)
  - (a) Carcinoma proved (12 cases)
  - (b) Carcinoma probably missed (2 cases)
  - (c) Carcinoma probably not present (2 cases)
  - (d) Other diseases proved (2 cases)
    - Congenital cystic disease
    - Cavernous hemangioma
- 2 Jaundice (12 cases)
  - (a) Catarrhal icterus (4 cases)
  - (b) Coarse nodular cirrhosis (2 cases)
  - (c) Obstructive jaundice (5 cases)
  - (d) Unclassified (1 case)
- 3 Cirrhosis of the liver (3 cases)
- 4 Miscellaneous (2 cases)

There are many patients with hepatomegaly who are suspected of having metastatic carcinoma but in whom the primary site cannot be established by the usual methods. In the past these patients have been routinely subjected to unnecessary exploration. In the majority of instances the diagnosis of carcinoma can be established definitely by hepatic aspiration, thus eliminating the attendant operative risk. Conversely, the finding of conditions other than a malignant growth will render the prognosis more favorable.

In cases in which carcinoma is suspected it has been found that occasionally as many as three aspirations are necessary before the diagnosis can be substantiated, since small metastases may easily be missed by the aspirating needle.

Four patients with catarrhal jaundice had hepatic aspiration performed. Only 1 of these showed definite pathologic changes by the routine methods of staining. In this instance the procedure was performed on the ninth day of jaundice. In the other cases aspiration was performed three to six weeks after the onset of jaundice and showed no definite abnormalities. Although the group is far too small to permit the drawing of any conclusions concerning the pathologic picture

of catarrhal jaundice, there is suggestive evidence that the parenchymal changes do not persist for more than a few weeks, even though the icteric index remains elevated

The patients for whom a diagnosis of coarse nodular cirrhosis was made had been icteric for four or five months. The hepatic function tests showed considerable hepatic damage. The specimens obtained by hepatic aspiration showed parenchymal degeneration, thickening, fibrosis and acute and chronic inflammation of the periportal fields. Occasionally inspissated bile was seen in the bile capillaries.

In the 5 cases of obstructive jaundice there were inspissated bile in the bile capillaries and acute and chronic cholangiolitis. There was no fibrosis or degeneration of the parenchyma of the liver. In all the cases, carcinoma of the head of the pancreas was suspected. At operation in 1 case, primary carcinoma of the gallbladder was present, the obstruction of the common bile duct being caused by a metastatic lymph node.

There was 1 case of unexplained anemia, in a 78 year old man with hepatomegaly. On one occasion, after a transfusion reaction, he became icteric for about two weeks. The jaundice was not hemolytic, and the anemia was shown to be aplastic by bone marrow examination. Hepatic aspiration on three occasions showed hemosiderosis and occasionally inspissated bile in the bile capillaries. The case still constitutes a diagnostic problem.

It has been observed that the specimens of hepatic tissue obtained by aspiration in cases of cirrhosis do not show sufficient structural detail to warrant the diagnosis of cirrhosis. Apparently the parenchymal tissue is aspirated easily enough, but the tough, fibrous tissue stroma is largely left behind. However, the procedure is still indicated in what may appear to be a case of typical cirrhosis, as the signs and symptoms may be confused with those of carcinoma.

In the study of hepatic disease, laboratory procedures can only reflect the alterations in function produced by the primary disturbance and are open to error in interpretation. Hepatic aspiration, on the other hand, may yield direct information about the pathologic changes in the liver. It offers a safe, rapid, inexpensive and reliable method of reaching the correct diagnosis and in some cases the only means of studying the pathologic changes associated with certain hepatic diseases. By its use many patients have been spared the ordeal of a useless laparotomy.

#### SUMMARY

Forty-eight hepatic aspirations have been performed on 35 patients. There have been no serious complications after the employment of this procedure.

The subcostal approach is preferred to the intercostal route, in order to obviate the danger of hemorrhage

In 1 case a small piece of colonic mucosa was recovered, owing to penetration of the colon. There were no untoward results

Hepatic aspiration has been of great value in the diagnosis of metastatic carcinoma and in the differential diagnosis of jaundice. It is also of value in the diagnosis of less common diseases, such as congenital cystic disease, cavernous hemangioma and schistosomiasis. It has been found of little value in the diagnosis of cirrhosis

NOTE—Since this paper was submitted for publication there has been 1 death directly attributable to the procedure. The case was that of a man with extensive metastatic carcinoma of the liver. Death was due to a small rent in the surface, measuring about 1 cm. This resulted in an exsanguinating hemorrhage

# RELATION OF CARDIAC OUTPUT TO CONGESTIVE HEART FAILURE

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Few studies relating to cardiac output in the presence of congestive failure have been made by acceptable technical methods. Lauter,<sup>1</sup> employing the direct Fick method in 3 cases of cardiac decompensation, found markedly subnormal values for the cardiac output and especially for the output per beat. Employing a similar technic, McGuire, Hauenstein and Shore<sup>2</sup> studied 5 cases of organic heart disease. Of these cases, decompensation was severe in 1, mild in 2 and slight in 1. In the case of severe failure the cardiac output was normal, a finding we have rarely encountered in patients subsequently studied by the acetylene method.

Harrison<sup>3</sup> investigated the cardiac output with the three sample acetylene method in 19 cases of congestive failure. He concluded

Persons with congestive heart failure may, and often do, have diminished circulatory minute volume. There is *no* correlation between the clinical state on the one hand and either the output of the heart per minute or the arteriovenous oxygen difference on the other.

Kinsman, Moore and Hamilton,<sup>4</sup> employing their dye injection method, found that the majority of patients with cardiac failure had a

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1 Lauter, S. Kreislaufprobleme, Munchen med Wchnschr **77** 526, 1930

2 McGuire, J., Hauenstein, V., and Shore, R. Cardiac Output in Heart Disease Determined by the Direct Fick Method, Including Comparative Determinations by the Acetylene Method, Arch Int Med **60** 1034 (Dec) 1937

3 Harrison, T. R. Failure of the Circulation, Baltimore, Williams & Wilkins Company, 1936, p. 64

4 Kinsman, M., Moore, J. W., and Hamilton, W. F. Studies on the Circulation. Analysis of Some Problems of the Circulation in Man in the Normal and in Pathological States by the Use of the Injection Method, Kentucky M J **31** 285, 1933, personal communication to the authors

decreased cardiac output. Starr and his co-workers,<sup>5</sup> employing their modification of the ethyl iodide method, reported decreased cardiac output for patients who had recovered from cardiac failure, as did Altschule and Volk,<sup>6</sup> who used the acetylene method.

Thus it is evident that no uniformity of opinion exists regarding the relation of cardiac output to congestive heart failure. It was the purpose of this study to determine if any correlation exists between the cardiac output and the degree of failure, as evidenced by the clinical picture and as measured by vital capacity, velocity of the flow of blood and level of venous pressure. Twenty patients with varying degrees of congestive heart failure were studied in this series. Repeated studies of certain of these patients who regained compensation will be reported later.

#### METHOD

The vital capacity was measured by the standard established by Blumgart and Weiss.<sup>7</sup> The circulation time from arm to carotid sinus was studied in the majority of patients by the cyanide method of Robb and Weiss.<sup>8</sup> Whenever decholin or saccharine was employed this is indicated in the tables. Venous pressure in the cubital vein was determined by the direct method of Moritz and Tabora.<sup>9</sup> Fluoroscopic examination of the heart was made in all cases, with especial reference to the amplitude of excursion of the cardiac borders.

The acetylene method of Grollman,<sup>10</sup> as modified by Grollman, Friedman, Clark and Harrison<sup>11</sup> for use in the presence of pulmonary congestion, was employed.

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5 Starr, I., Donal, J. S., Margolies, A., Shaw, R., Collins, L. H., and Gamble, C. J. Studies of the Heart and Circulation in Disease. Estimations of Basal Cardiac Output, Metabolism, Heart Size and Blood Pressure in Two Hundred and Thirty-Five Subjects, *J. Clin. Investigation* **13** 561, 1934.

6 Altschule, M. D., and Volk, M. C. Therapeutic Effect of Total Ablation of Normal Thyroid on Congestive Failure and Angina Pectoris. XVIII The Cardiac Output Following Total Thyroidectomy in Patients With and Without Congestive Heart Failure, with a Comparison of Results Obtained with the Acetylene and Ethyl Iodide Methods, *Arch. Int. Med.* **58** 32 (July) 1936.

7 Blumgart, H. L., and Weiss, S. Clinical Studies on the Velocity of Blood Flow. X The Relation Between the Velocity of Blood Flow, the Venous Pressure and the Vital Capacity of Lungs in Fifty Patients with Cardiovascular Disease Compared with Similar Measurements in Fifty Normal Persons, *J. Clin. Investigation* **5** 379, 1928.

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10 Grollman, A. The Cardiac Output of Man in Health and Disease, Springfield, Ill., Charles C. Thomas, Publisher, 1932.

11 Grollman, A., Friedman, B., Clark, G., and Harrison, T. R. Studies in Congestive Heart Failure. XXIII A Critical Study of Methods for Determining the Cardiac Output in Patients with Cardiac Disease, *J. Clin. Investigation* **12** 751, 1933.



for the determination of the cardiac output in all cases. Oxygen consumption was determined in all cases with the Benedict-Roth metabolism apparatus.

The fundamental principles underlying the acetylene method were described by Grollman as follows:

"If one inspires a mixture containing a foreign gas (i e., a gas not normally present in the body) this gas will enter the blood stream and be carried to the tissues. If the gas possesses certain physical properties, as regards its solubility and diffusibility, it will distribute itself between the alveolar air and the blood in accord with the physical laws of the solution of gases in liquids. According to this law the volume of the gas dissolving in the liquid will be proportional to its tension above the liquid. A knowledge of the solubility of the gas in the liquid allows us to calculate the amount which will dissolve per unit volume of liquid when the gas is at any given tension. Conversely by measuring the amount of gas dissolved in the liquid and its tension above the liquid, we can calculate the amount of liquid which has been brought into equilibrium with the gas. This is the fundamental idea underlying the determination of the cardiac output by the foreign gas principle. The blood flowing through the lungs enters into equilibrium with a foreign gas. The tension and rate of absorption of this gas are determined, from which in turn is calculated the volume of blood flowing through the lungs in unit time. Since, except in certain rare congenital anomalies, all the blood pumped by the heart passes through the lungs, we are thus determining the cardiac output."

The patients selected for study had entered the hospital because of the symptoms associated with congestive heart failure. No patients with such complicating factors as anemia, advanced emphysema or fever, as determined by mouth, were examined. Owing to the fact that the procedure associated with this method for measuring cardiac output requires the cooperation of the subject, we were unable to study patients with cardiac asthma or with dyspnea severe enough to prevent cooperation. However, as soon as the decrease in dyspnea made the rebreathing procedure possible, the subjects were trained, and the cardiac output was determined on the following morning. The vital capacity, venous pressure and circulation time were measured the same morning. All determinations were made under basal conditions. The patients without exception were receiving digitalis at the time the studies were made. The majority of investigators have expressed the belief that digitalis increases or has no constant influence on the output of the dilated heart with regular rhythm.<sup>12</sup>

Two values for the arteriovenous oxygen differences were obtained in each case from analyses of the three samples collected during rebreathing. Inadequate mixture in the lung-bag system resulting from pulmonary congestion and errors due to recirculation were minimized by discarding all determinations when the arteriovenous oxygen differences between samples 1 and 2 and 2 and 3 differed

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<sup>12</sup> Stewart, H J, and Cohn, A E. Studies on the Effect of the Action of Digitalis on the Output of Blood from the Heart. II. The Effect on the Output of Hearts in Heart Failure with Congestion in Human Beings, *J Clin Investigation* **11** 917, 1932. Harrison, T R. Failure of the Circulation, Baltimore, Williams & Wilkins Company, 1936. Starr, I, Gamble, C J, Margolies, A, Donal, J S, Joseph, N, and Eagle, E. A Clinical Study of the Action of Ten Commonly Used Drugs on Cardiac Output, Work and Size, on Respiration, on Metabolic Rate and on the Electrocardiogram, *J Clin Investigation* **16** 799, 1937.

by more than 10 per cent, save for 2 patients (cases 10 and 14), whose differences were 12.5 per cent and 1 patient (case 19) for whom the arteriovenous oxygen difference between samples was 15 per cent

In evaluating the severity of failure three physicians classified the patients as showing 1 plus, 2 plus, 3 plus and 4 plus degrees of failure on the basis of the clinical findings. These physicians were not familiar with the results of the measurements of cardiac output and were consequently unprejudiced in their effort to classify appropriately the condition of each patient. Nine of the patients studied in this series died. Nine are living, 5 of whom are cardiac invalids and 4 are able to work. The 2 remaining patients cannot be traced.

TABLE 1—*Determinations of Cardiac Output for Sixteen Normal Subjects*

Patient	Arterial Blood Pressure, Mm Hg	Vital Capacity, Percent age of Normal	Basal Metabolic Rate	Arteriovenous Oxygen Difference, Cc per Liter	Cardiac Output		Comment
					Liters per Square Meter	Cc per Beat	
1	130/ 80	53	— 3	46.4	2.59	56	Rheumatoid arthritis
2	120/ 80	100	—10	67.5	1.84	39	Normal
3		97	—10	64.8	1.93	40	Normal
4		70	+12	59.2	2.39	47	Normal
5	140/ 80	97	— 6	65.2	1.96	49	Convalescent from phenobarbital poisoning
6	108/ 70	107	— 9	59.2	2.14	75	Hemophilia
7	100/ 70	113	— 4	65.8	2.02	51	Normal
8	140/110	97	— 3	57.9	2.32	51	Convalescent from hernioplasty
9	110/ 80	93	— 1	76.2	1.80	36	Normal
10	110/ 74	100	—15	62.5	1.90	40	Convalescent from varicosectomy
11	100/ 70	89	— 6	58.5	2.18	63	Convalescent from hernioplasty
12	140/100	90	— 3	56.0	2.21	50	Peripheral neuritis with foot drop
13	120/ 80	85	— 5	73.3	1.70	44	Convalescent from hernioplasty
14	98/ 78	96	—12	62.3	1.96	50	Normal
15	110/ 70	73	— 1	52.5	2.35	42	Neurocirculatory asthenia
16	120/ 90	111	+15	68.2	2.33	52	Normal
Average				62.2	2.10	49	

## RESULTS

Comparative studies with the acetylene and the direct Fick method have shown close parallelism of results in cases of decompensation under basal conditions, although the absolute values were lower with the acetylene method.<sup>2</sup>

We believe, therefore, that the results to be described are significant, but realize that probably no indirect method of measuring cardiac output is accurate to the cubic centimeter.

Table 1 summarizes the data concerning 16 normal subjects. The mean value for cardiac output in this group was  $2.16 \pm 0.03$  liters per square meter of body surface per minute. The coefficient of variability was 10 per cent.

Table 2 summarizes the data concerning 20 patients with congestive heart failure. The mean value for cardiac output in this group was

TABLE 2—Circulatory Studies of Twenty Patients with Congestive Heart Failure

Patient	Age	Diagnosis	Arterial Blood Pressure, Mm Hg	Clinical Degree of Failure	Dyspnea	Edema	Vital Capacity, Percent of Normal	Circu- lation Time, Sec *	Venous Pressure, Cm of Water	Basal Metabolic Rate, Percentage of Normal†	Arterio- venous Oxygen Difference, Cc per Liter‡	Cardiac Output, Liters per Square Meter‡	Cardiac Output per Beat, Cc
1	46	Syphilitic aortitis with aortic insufficiency	130/68	+	++	+	53	39	9.0	+10	92.6 96.5	1.53	34.0
2	61	Arteriosclerotic and hypertensive heart disease	150/100	++++	+++	+++	23?			—9	119.0 110.0	0.91? 1.62	13.5 32.0
3	49	Arteriosclerotic heart disease with hypertension	150/110	+++	+++	+	42	23	10.6	+20	94.5 100.0	1.62	32.0
4	50	Arteriosclerotic and hypertensive heart disease	160/130	+++	+++	++	40	40 (D)	14.0	+8	116.0 107.0	1.24	19.0
5	36	Rheumatic heart disease, mitral stenosis, auricular fibrillation	130/85	++	++	+	37	38 (D)	15.0	+13	120.0 127.0	1.35 1.58?	21.0 29.0
6	75	Arteriosclerotic and hypertensive heart disease, pulmonary emphysema	140/100	++++	++++	++++	35		16.0	+34?	95.5 93.5	1.58?	29.0
7	49	Aortic insufficiency, syphilitic aortitis	210/10	++	++	++	35			+42	79.7 83.5	2.27	40.0
8	27	Cardiac dilatation and hypertrophy, tuberculous pericarditis without con- striction (autopsy)	110/74	+++	+	+++	40			+20	123.0 140.0	1.11	17.0
9	38	Rheumatic heart disease, mitral stenosis, aortic insufficiency	110/68	+	0	+	68	25 (D)	4.0	+20	79.0 80.3	2.04	49.0
10	47	Arteriosclerotic and hypertensive heart disease	160/120	++	++	0	42	32 (D)	9.0	+23	120.0 105.0	1.43 0.73?	36.0 12.4
11	52	Syphilitic aortitis	120/80	+++	+	+++	29?	43 (S)	18.0	—19?	148.0 135.0		
12	56	Hypertensive and coronary heart disease	130/115	+	+	0	55			—6	59.0 53.7	2.09	40.0
13	41	Syphilitic and hypertensive heart disease, aortic insufficiency	170/70	+++	++	++	63	30	5.0	+19	87.0 85.0	1.82	39.0
14	41	Coronary heart disease, hyper- tension	140/115	++	++	+	73	20	6.3	+14	91.0 104.0	1.40	23.0
15	39	Syphilitic heart disease, aortic insufficiency	150/40	+++	+++	+++	33	43	11.5	+14	136.0 137.0	1.13	16.3
16	47	Arteriosclerotic and hypertensive heart disease	130/110	+++	+++	+++	48	31 (D)	13.0	+20	134.5 125.2	1.20?	22.0
17	49	Syphilitic aortitis, aortic insufficiency	140/36	++	++	0	70	34		+12	91.0 88.4	1.63	29.0
18	44	Arteriosclerotic and hypertensive heart disease	120/100	++	+++	0	57	44	8.5	—7	110.0 112.0	1.11	21.0
19	67	Syphilitic and arteriosclerotic heart disease with aortic insufficiency	140/50	++	++	++	71	39		—13	94.0 80.0	1.21	25.0
20	50	Arteriosclerotic and hypertensive heart disease	160/130	+++	+++	+++	36	52		+11?	120.0 111.0	1.45?	21.0

\* D indicates decholin S indicates saccharine in all other cases sodium cyanide was used

† The question mark indicates that edema prevented precise determination of the body surface

‡ The two values are the differences between samples 1 and 2 and 2 and 3 respectively

$1.52 \pm 0.06$  liters per square meter per minute. The coefficient of variability was 27.3 per cent. The reference to the ratio between the means and their respective probable errors indicates that both samples were large enough to afford stable means.

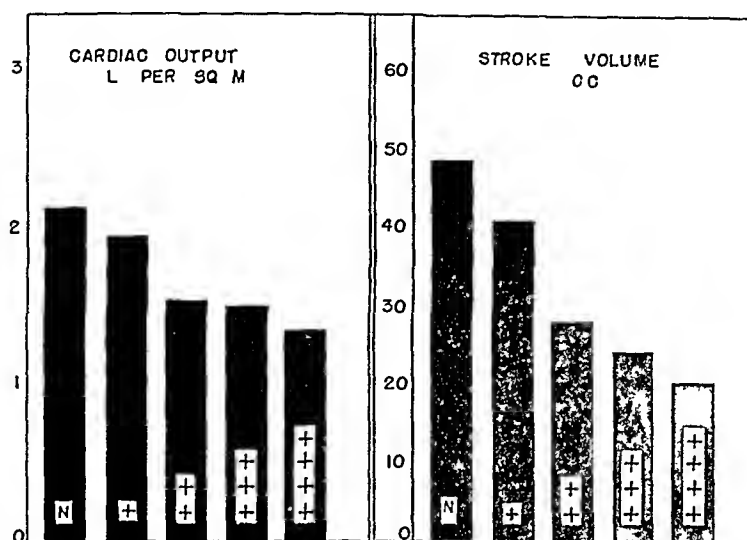


Chart 1—The cardiac output and stroke volume as related to the degree of congestive heart failure. *N* indicates the normal group, plus signs indicate the degree of heart failure.

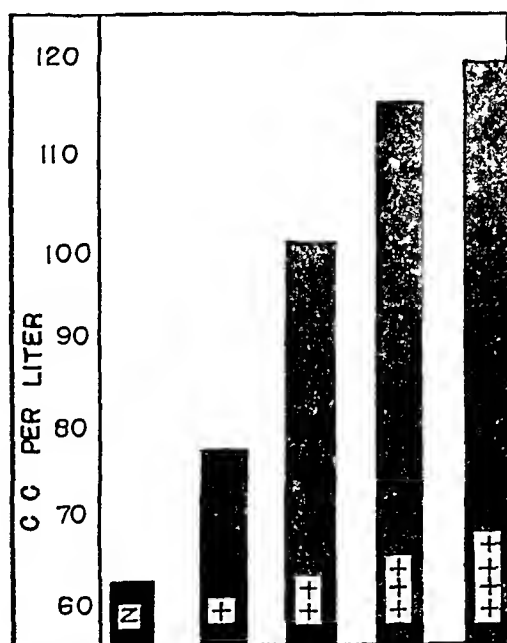


Chart 2—The arteriovenous oxygen difference as related to the degree of congestive heart failure. *N* indicates the normal group, plus signs indicate the degree of heart failure.

The difference between the two groups,  $0.64 \pm 0.072$  liters per square meter of body surface, is a statistically significant difference—about nine times its own probable error.

The output per beat (stroke volume) for the subjects with decompensation was reduced, averaging 27 cc, while for the control subjects the average stroke volume was 49 cc

While no sharp differentiation was observed among the patients with severe failure, the average values for cardiac output steadily diminished as the degree of failure increased. In the control group the output per square meter per minute averaged 2.1 liters, in the group with 1 plus failure, 1.88 liters, in the 2 plus group, 1.48 liters, in the 3 plus group, 1.44 liters, and in the 4 plus group, 1.34 liters.

Likewise, a decrease in stroke volume was observed with progressive increase in the gradation of failure. In the control group the average output per beat was 49 cc, in the 1 plus group, 41 cc, in the 2 plus group, 28 cc, in the 3 plus group, 24 cc, and in the 4 plus group, 21 cc.

These data are illustrated by chart 1.

In the control subjects the average arteriovenous oxygen difference was 62.2 cc per liter, while in the 1 plus group of patients with cardiac disease the average value was 76.3, in the 2 plus group 100, in the 3 plus group 114 and in the 4 plus group 118 cc per liter. These results are indicated graphically in chart 2.

#### COMMENT

In this series of 20 patients with decompensation there was a trend toward decreased cardiac output in the patients with congestive failure. When considered from the standpoint of output per square meter of body surface, this was even more striking when related to output per beat. The feeble pulsations of the hearts of the patients with a small cardiac output as seen by fluoroscopic examination afforded convincing visual proof of the low values. The increasing arteriovenous oxygen difference in the patients with more severe decompensation is likewise significant and is further evidence of the sluggish circulation of these patients.

From statistical analysis no smooth correlation between the level of the cardiac output and the degree of decompensation was observed. At the extremes—that is, in the 1 plus group and the 4 plus group—there was the definite suggestion of relation between the clinical state of the patient, on the one hand, and the level of the cardiac output and the arteriovenous oxygen difference on the other.

In only 1 case (case 7) was the cardiac output normal in the presence of congestive failure. The fact that overlapping of subnormal and normal values occasionally occurs is not surprising, since several factors which cause an increase in the cardiac output of normal persons are frequently present in association with cardiac decompensation: (1) exercise associated with hyperpnea, (2) the excitement and anxiety often present with severe decompensation, (3) long standing anoxemia of the tissues, (4) increased metabolism, (5) increased venous pressure and

(6) low grade fever Thus several factors of importance in elevating the cardiac output are often operating simultaneously in many patients with decompensation Yet, despite these stimuli, the cardiac output tends to be subnormal In other words, because of the physical exercise associated with hyperpnea we doubt the truly "basal" state of the patients with cardiac decompensation and therefore believe that the low values for the majority of these patients are even more significant than our results indicate

From personal communication with other physicians interested in the relation of congestive heart failure to the cardiac output, it is our opinion that the cases of 3 plus and 4 plus failure studied in this series may represent instances of more advanced myocardial damage than those in a previous series<sup>13</sup> For this reason the lack of complete agreement with another report<sup>14</sup> may indicate a difference in selection of patients rather than differing results with similar technic

#### SUMMARY

In 19 of 20 cases of congestive heart failure the cardiac output was subnormal, the mean value being  $1.52 \pm 0.06$  liters per square meter per minute, while in control cases the mean was  $2.16 \pm 0.03$  liters

In the groups of patients with congestive failure of varying severity there was a trend toward reduction of cardiac output with the severer manifestations of failure

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13 Harrison, T. R. Personal communication to the authors

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# SPONTANEOUS ARTERIOVENOUS ANEURYSMS OF THE THORAX

A REVIEW OF THE LITERATURE, WITH A REPORT OF TWO CASES

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LOS ANGELES

Beavor, in 1832, was the first to describe spontaneous arteriovenous aneurysm of the thorax. Since that time there have been but two comprehensive reviews of the reported cases, Pepper and Griffith making the first, in 1890. These authors not only collected reports of 28 cases and added 1 of their own but laid down diagnostic criteria that have never been surpassed. In 1925 the second detailed review appeared, when Shennan reported 2 cases of his own and collected reports of 72 others. In the latter report a short summary of each case was given whenever the clinical record was accessible.

Since 1925 a number of authors have reported cases, with references to the literature, bringing the total number of cases to 98. We are adding 2 cases of our own and reports of 79 others in which the records are available, 24 of which were not included in either previous analysis.

The fact that only 2 cases of spontaneous arteriovenous aneurysm of the thorax have been discovered at the Los Angeles County Hospital in 19,000 autopsies further emphasizes the rarity of this condition. In addition, 1 case was reported from this hospital in 1935 by W. E. Graham and Samuel Weiss, the autopsy having been performed by the county coroner. A total of 192 cases of aneurysm of the aorta were found among the 19,000 autopsy reports mentioned, 144 of the patients having syphilis and 48 having arteriosclerosis.

## SUMMARY OF CASES

*Age and Sex*—The age and sex were mentioned in 80 of the 81 cases in which the records were accessible. The age incidence according to decades was as follows:

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From the Department of Medicine of the College of Medical Evangelists and from the Los Angeles County Hospital

Decades	Men	Women
20-30	1	0
30-40	13	0
40-50	21	4
50-60	30	3
60-70	7	1
	—	—
Total	72	8—80

As expected, the majority of the patients were men, only 10 per cent being women. The greatest age incidence was between 50 and 60 years, 40 per cent of the patients being in this age group, while 72 per cent were between 40 and 60 years of age.

*Etiologic Factors*—The data relative to the etiologic factors are as follows:

### 1 Syphilis

- (a) History only (26 cases)
- (b) Positive serologic evidence (11 cases)
- (c) Autopsy evidence (9 cases)
- (d) Doubtful evidence (9 cases)

2 Arteriosclerosis, rheumatic fever and typhoid were mentioned as possible causes.

We feel that the percentage of cases of aneurysm due to syphilis is too low (less than 50 per cent) because of the fact that serologic tests have been in use only since 1906. Another factor is that many patients died before an adequate history and laboratory tests could be obtained. It is interesting to note that since 1925 reports of 26 cases have been collected, in 20 of which (77 per cent) there was definite evidence of syphilis, either serologically or anatomically. In this group of 26 cases, there was no autopsy in 2 cases and no access to the records in 1 case. Not including these 3 cases, there was positive evidence of syphilis in 87 per cent of the cases.

*Exciting Cause of the Perforation*—Evidence indicates that physical strain and emotional stress or agitation are the exciting causes of perforation in a large number of cases. It is also true that there are a few cases in which neither of these is a factor.

*Symptoms and Physical Signs*—There were 80 cases in which the symptoms and signs were mentioned:

Symptoms and Signs	Number of Cases
Cyanosis	80
Swelling	79
Suddenness of onset	50
Dyspnea	35



Symptoms and Signs	Number of Cases
Unconsciousness	16
Pain	15
Orthopnea	9
Tightness of neck and head	8
Dysphagia	6

Cyanosis and swelling limited to the distribution of the tributaries of the superior vena cava were constant findings. One patient died before swelling could develop. There was suddenness of onset in 62 per cent of the cases, making this an important point in the differential diagnosis.

On physical examination a large number of patients showed evidence of tumor in the thorax, that is, dulness below the right clavicle and behind the upper portion of the sternum. Occasionally a thrill was detected in this area. The veins over the thorax and abdomen were enlarged in 44 cases. Pulsation was noted in 12.

Cardiac murmurs were mentioned 77 times. In 30 cases the characteristic murmur was found, in 22 a double murmur, in 18 a systolic murmur alone and in only 1 a diastolic murmur. There were no murmurs in 6 cases. Either the characteristic murmur or a double murmur marked 67 per cent of the cases.

*Length of Survival After Perforation*—The data regarding survival after perforation were as follows:

Survival	Number of Cases	Survival	Number of Cases
Immediate death	3	Up to 1 week	24
Less than 12 hours	4	1 week to 1 month	30
Less than 24 hours	5	1-2 months	14
1-2 days	2	Over 2 months	13
2-3 days	2		—
3-7 days	8	Total	81
		Recovery (patient alive at time of report, cases 20, 60, 97)	3

*Position of Perforation, Relation to Azygos Vein, Size of Aneurysm*—In 81 cases the perforation was discussed. Perforations were double in 7 of these and triple in 3 others.

The relation of the perforation to the azygos vein was mentioned in 73 cases. In 41 cases the perforation was above the azygos vein, and in 4 of these it was in the terminal part of the innominate vein. Nine perforations were opposite the opening of the azygos vein, 18 were between the azygos vein and the right auricle and 2 were at the entrance to the auricle, in 3 cases the communication was with the right auricle. In those cases in which the perforation was above the azygos vein, the swelling and cyanosis were more or less limited to the head, neck and upper extremities, whereas in those cases in which it was

below or opposite the azygos vein, there were, in addition, swelling of the walls of the thorax and hydrothorax, with late extension to the lower extremities

The average diameter of the aneurysm was about 8 cm. The smallest measured about 4.5 by 5 cm, and the largest was 16 cm in diameter. The origin was in the ascending arch of the aorta.

*Treatment*—The only treatment is symptomatic and supportive, in the attempt to maintain life until collateral circulation can be established. This evidently occurred in the 3 patients who are reported as having recovered or as still living.



Fig. 1 (case 1)—Infra-red photograph taken about one week before death. The edema and cyanosis, ending at the costal margin in a collar of venules, with the development of collateral circulation, are apparent.

#### CASE REPORTS

**CASE 1**—Mr. T. J. B., aged 58, single, a Caucasian, was admitted to the Los Angeles County Hospital on Feb. 13, 1936. He complained of inability to sleep on his left side and back and precordial pain radiating to the left shoulder and arm for three years. For three weeks he had noted swelling and cyanosis of the face and neck.

*History*—The patient first had difficulty in sleeping when lying flat on his back or on his left side. This symptom was gradual in onset and had progressed to the point where it was impossible for him to sleep unless he sat upright in bed. Almost simultaneously with the appearance of positional insomnia, the patient began to notice pain in the precordial region, which at first was brought on by

exertion and which radiated to the shoulder and arm. This condition gradually became worse, so that at the time of entry he felt pain with the slightest exertion. A sense of tightness in the throat associated with swelling and cyanosis of the head and neck had developed three weeks prior to entry. This gradually produced dyspnea. The cyanosis was limited to the head, neck and thorax.

The past history was essentially unimportant with the exception of a penile chancre, which occurred when he was 28 and which had been inadequately treated. The family history was not significant.

*Physical Examination*—Physical examination revealed a well developed and well nourished man in an orthopneic position. He was dyspneic and exhibited marked cyanosis and swelling of the face, neck and thorax. The temperature was 98 F, the pulse rate 88 and the respiratory rate 20. He weighed 165 pounds (74.8 Kg) and was 67 inches (170.18 cm) tall. The pupils were equal and reacted to light and on convergence. The fundi were normal except for dilated vessels and cyanosis. The ears showed cyanosis but no changes in the tympanic membrane. There was marked congestion of the pharynx and nasal passages, with cyanosis of the mucous membrane. The teeth were carious. The tonsils were small and buried. The neck was swollen, tense and cyanotic, with pitting on pressure, which was more marked on the right side. There were no pulsating vessels. The chest showed cyanosis and swelling, which extended to the costal margin, ending in a collar of distended venules. The left border of cardiac dullness was found to be in the fifth interspace at the midclavicular line. The right border was 3 or 4 cm to the right of the sternum in the second intercostal space. The cardiac rhythm was regular. A loud systolic murmur was heard best at the second interspace on the right, a diastolic murmur was heard over the same area. The blood pressure in the left arm was 150 systolic and 30 diastolic, in the left leg, 180 systolic and 50 diastolic, in the right arm, 145 systolic and 30 diastolic, and in the right leg, 200 systolic and 55 diastolic. The pulse was of the Corrigan type. A pistol shot and the Duroziez sign were heard over the femoral arteries. Examination of the lungs and abdomen revealed no abnormality. Cyanosis and edema were noted in both upper extremities, being more marked in the right than in the left. The lower extremities were normal. Neurologic and glandular examinations revealed normal conditions.

*Laboratory Examination*—The Wassermann and Kahn tests of the blood gave a positive reaction. Examination of the blood showed erythrocytes, 4,100,000, hemoglobin, 65 per cent, leukocytes, 9,150, neutrophils, 76 per cent, lymphocytes, 20 per cent, and monocytes, 4 per cent. The urine was normal.

*Roentgenographic Study*—The cardiac silhouette was essentially normal. There was an aneurysm of the ascending and transverse aorta, with marked enlargement of the ascending aorta. The pulmonary fields were clear.

*Electrocardiographic Study*—Moderate slurring of the QRS complex was present in the standard leads. The voltage was low in leads I and III. Lead IV showed considerable slurring of the QRS, and the T wave tended to be diphasic. The conclusion was reached that there were myocardial impairment and coronary disease.

*Clinical Diagnosis*—The clinical diagnosis was syphilitic heart disease and aneurysm of the ascending aorta, with compression of and perforation into the superior vena cava.

*Course*—The patient's condition remained about the same except for increasing dyspnea and pain in the throat. Occasionally he awakened with a sensation of strangulation. The first marked change in his condition was noted on March 15,



Fig 2 (case 1) —Roentgenogram showing aneurysm of the ascending aorta

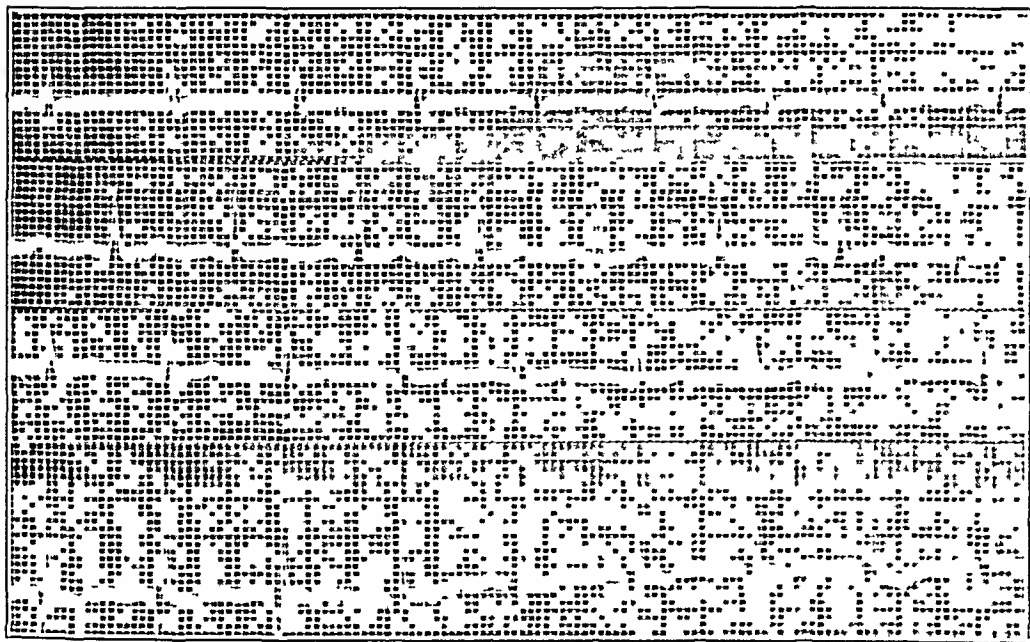


Fig 3 (case 1) —Electrocardiogram taken with the patient lying down (resistance, 400 ohms, auricular rate, 110, ventricular rate, 110, PR interval, 0.16 second, rhythm, regular)

when he had a smothering attack, the cyanosis became more intense and the dyspnea more marked. From this time on it was necessary to give him oxygen. The following day it was noted that the veins over the abdomen were beginning to distend and to pulsate. The character of the cardiac murmur also changed, becoming louder and more whirring, so that it was continuous. On March 23 moist rales developed in the lungs. Because of the striking pulsation in the veins, Dr R. Manning Clarke suggested the diagnosis of an arteriovenous communication. The pressure in the pulsating veins was measured and found to be 22 cm of water, the water pulsating in the manometer 2 or 3 mm. The oxygen tension of the blood in the pulsating veins on the abdomen was 10.8 per cent and the tension in the veins of the lower extremities 10.4 per cent. These differences were not sufficient to be of significance. From March 28 to April 2 the patient rapidly grew worse, with the development of congestive heart failure, resulting in ascites, hydrothorax and extension of edema to dependent portions. During this time the patient failed to respond to any medication and died suddenly on April 2, while being moved about in bed.

The treatment administered was symptomatic, morphine, ice bags, digitalis and oxygen being used.

*Autopsy*.—An autopsy was performed by Dr Albert F. Brown. There were marked generalized pitting edema and lividity above the level of the epigastrium. The pupils were equal and regular. The right testicle was slightly enlarged and indurated. Superficial veins were not visible. The skull and central nervous system were normal.

The heart weighed 390 Gm. The pericardial sac contained 50 cc of clear fluid. The surfaces were smooth. The wall of the left ventricle was 14 mm thick, that of the right ventricle, 6 mm thick. Each chamber was moderately dilated. The circumference of the tricuspid valve was 12.5 cm, that of the pulmonic valve, 9 cm. One of its cusps was held rigidly into the lumen of the valve because of the complete occupation of its sinus by a hemispherical aneurysm of the adjacent aorta which was 1.5 cm in diameter. The circumference of the aortic valve was 9 cm. Its cusps were not appreciably altered, and the commissures were not widened. There was no evidence of incompetency. The coronary orifices were 1 cm above the upper margin of the valve. The left orifice was of normal caliber, while the right showed 50 per cent stenosis, beginning in the depths of a 5 mm hemispherical pouch. The remaining portions of the coronary arteries were normal. The ascending aorta from immediately above the coronary mouths to the first part of the arch was diffusely aneurysmal, the circumference being 12 to 15 cm. Its wall was thick, and the intima revealed the pearly plaques and wrinkling of syphilitic aortitis. The dilatation was chiefly posterolateral (right). Two secondary pouches and one perforation characterized the aneurysm. These satellite sacs were each 1.5 cm in diameter and hemispherical. One projected into the pulmonary valve, the other was in the anterior aspect of the aorta. The perforation, 12 mm in diameter, was located 6 cm above the aortic valve in the right posterolateral aspect. It opened directly into a localized intrapericardial sac, about 5 cm long and 2 cm in diameter, which lay between the aortic aneurysm and the superior vena cava, the latter vessel communicating with the pericardial pocket by means of a 7 mm perforation. Neither the aortic aneurysm, except for the small secondary pouches, nor the pericardial sac contained antemortem thrombus, only soft, dark red clot. The vena cava, aside from the perforation, seemed essentially unchanged, but the innominate veins contained small, adherent plaques of thrombi. The tributaries of these veins which were examined, viz, both subclavian and both internal jugular veins, the cephalic veins and the pectoral

veins, were occluded by antemortem thrombi. The occlusion was complete except in the right internal jugular vein, where about 50 per cent of the lumen remained patent. The thrombotic material was a dull gray-red and somewhat granular and occasionally showed beginning degeneration. The azygos veins were free from thrombi. The descending aorta revealed little, if any, evidence of syphilitic involvement, and the inferior vena cava appeared normal.

The right pleural cavity contained 1,500 cc and the left 1,200 cc of clear, amber fluid. The specific gravity was 1.016. At the apex of the right lung an

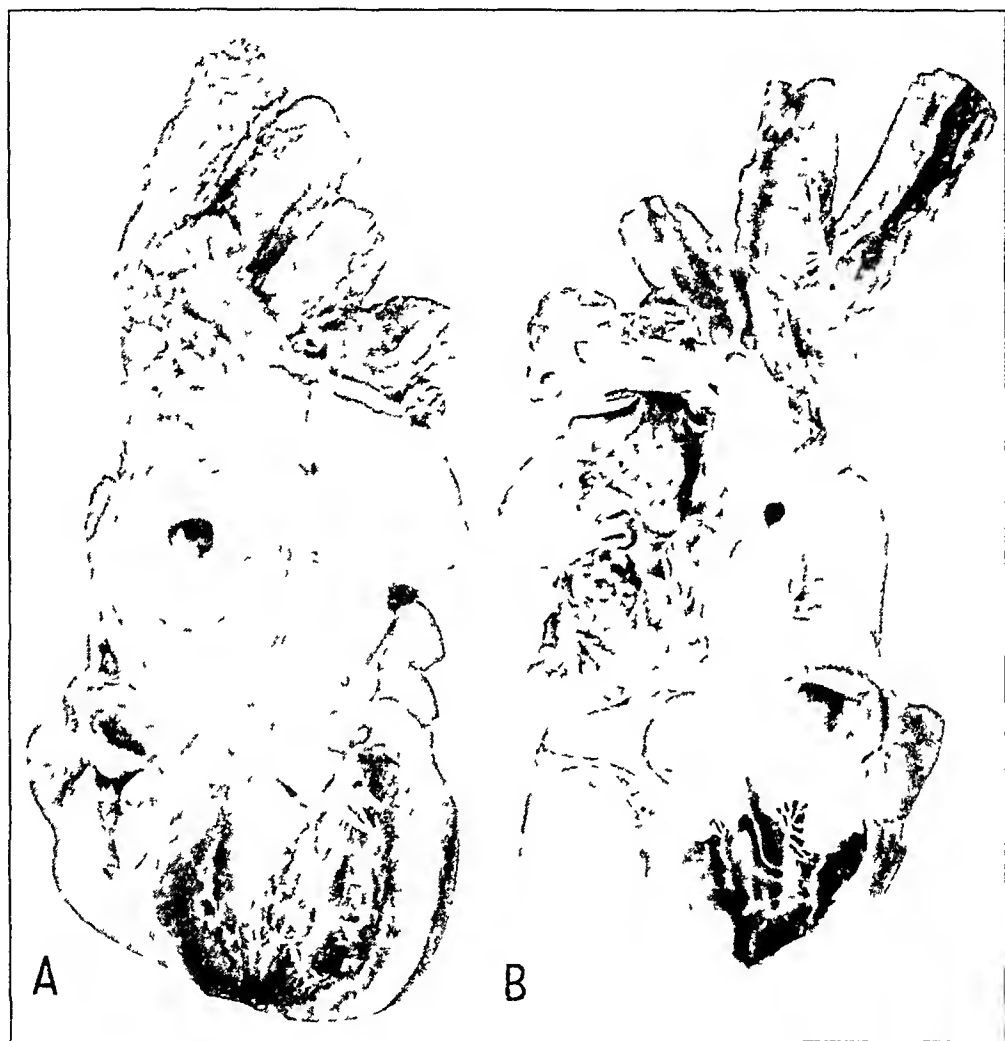


Fig 4 (case 1) —*A*, the heart is opened on the aortic side, showing the aneurysm with the perforation and the pericardial pouch between the aorta and the vena cava. *B*, the heart is opened on the side of the vena cava, showing the perforation into the superior vena cava and the thrombi in its tributaries.

old fibrous subpleural scar and old fibrous adhesions were present. The right lung weighed 750 Gm and the left lung 700 Gm. Each lung was edematous and posteriorly congested. The bronchial mucosa was slightly hyperemic. The lumen contained thin mucus. The pulmonary artery was normal.

The peritoneum and pancreas were normal. The peritoneal cavity contained 100 cc of clear fluid. There was slight passive congestion of the liver. The spleen and kidneys were normal.

The right testis was slightly enlarged and firm. The cut surface showed replacement of the substance of the testis by firm, pale white, translucent tissue, which was confluent nodular. The left testicle was normal.

Examination of the skeletal system revealed that the bodies of the fourth to seventh dorsal vertebrae were eroded to a depth of 5 mm on the right antero-lateral aspect because of the pressure of the aneurysm.

*Anatomic Diagnosis*—The anatomic diagnosis was (1) syphilitic aortitis, (2) a ruptured fusiform aneurysm of the ascending aorta, (3) stenosis of the pulmonary valve due to encroachment of the aortic aneurysm, (4) localized hemo-pericardium, (5) a fistula involving the aorta, pericardium and vena cava, (6) thrombosis of the great veins of the neck and upper extremity, and (7) gumma of one testicle.



Fig 5 (case 2) —Infra-red photograph showing the cyanosis and edema above the epigastrium, with the developing of the collateral circulation

**CASE 2**—Mr J R, aged 46, a Mexican, single, was admitted to the Los Angeles County Hospital on Feb 24, 1937. He complained of a brassy, nonproductive cough, with hoarseness and orthopnea, for one year. Cyanosis and swelling had been noted for three months prior to entry.

*History*—The patient was apparently well until one year before entry, when he acquired a brassy, nonproductive cough, with hoarseness, dyspnea and orthopnea but no fever. The cyanosis and swelling were first noticed three months before entry. They began in the right upper extremity and gradually extended to the head, neck, left upper extremity and thorax and down to the epigastrium and had increased in severity in the last four days.

A recent history revealed no abnormalities except the presenting illness. The patient had had gonorrhea and possibly chancre in his youth. The family history was not significant.

*Physical Examination*—The patient was a well developed and well nourished man in an orthopneic position. There were cyanosis and swelling of the head, neck, upper extremities and thorax. The temperature was 98.6 F, the pulse rate 88 and the respiratory rate 18. He weighed 174 pounds (78.9 Kg) and was 74 inches (188 cm) tall. The pupils were equal, and their reactions were normal. Except for cyanosis and swelling the ears, nose and mouth were normal. The cyanosis and edema extended down to the costal margin. The chest was barrel shaped, and dilated veins were present both anteriorly and posteriorly. The right border of cardiac dullness extended to the right midclavicular line in the second interspace. The apex beat and point of maximum intensity were in the sixth interspace in the left nipple line. Whurring systolic and diastolic murmurs were heard just below and to the right of the aortic area. The systolic phase was louder and harsher than the diastolic. Examination of the lungs showed dullness to flatness over the base of the right lung, with distant breath sounds, which were bronchovesicular. Moist rales could be heard throughout the right pulmonary field. The left lung was normal. Abdominal examination disclosed only dilatation of the superficial veins. Although the upper extremities were cyanotic and edematous, the lower extremities were normal. Neurologic and glandular examinations revealed no abnormality.

*Laboratory Examination*—A blood count disclosed erythrocytes, 4,240,000, hemoglobin, 76 per cent, leukocytes, 5,150, neutrophils, 76 per cent, lymphocytes, 15 per cent, monocytes, 8 per cent, and eosinophils, 1 per cent. The Wassermann and Kahn tests of the blood gave a positive reaction. The urine showed a 2 plus reaction for albumin but contained no pus.

*Roentgenographic Examination*—A large amount of abnormal density was seen in the lower part of the right pulmonary field, extending up along the lateral wall of the chest. A small amount of fluid was seen at the left costophrenic sulcus. The mediastinum at the level of the aortic arch was seen to be considerably expanded to the right, this expansion did not pulsate, and so far as could be ascertained through the fluid, it had the characteristics of a mediastinal tumor.

*Electrocardiographic Examination*—The QRS complex was small and slurred in all leads. It was concluded that there was myocardial impairment.

*Clinical Diagnosis*—The diagnosis was syphilitic aortic aneurysm perforating into the superior vena cava.

*Course*—The treatment was symptomatic. The patient grew worse rapidly and on the second day in the hospital showed pulsating veins on the thorax. On the fourth day he became manic. He climbed out of bed and, seizing a chair, broke two windows, whereon he immediately dropped dead.

*Autopsy*—Autopsy was performed by Dr J. M. Shachtman. There were cyanosis and pitting edema of the body above the costal margin. The skull and central nervous system were not examined.

The heart was apparently not enlarged. The tricuspid valve measured 11.5 cm in circumference. The leaflets were normal. The pulmonary valve measured 7.5 cm in circumference and appeared normal. The mitral valve measured 7 cm in circumference. The leaflets were thickened on the external margins and at the base. The chordae tendineae were thickened and shortened. The aortic valve measured 7 cm in circumference, and between two of the cusps there was a



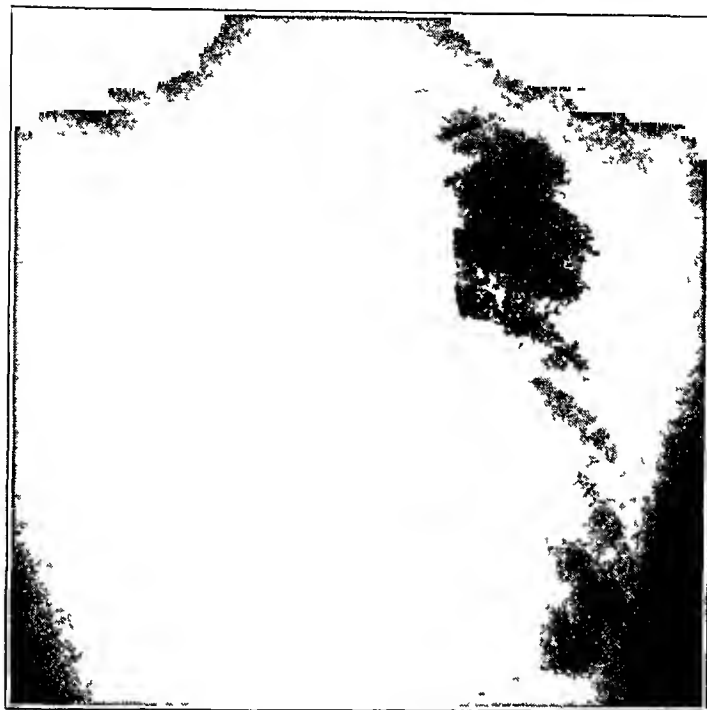


Fig 6 (case 2) —Roentgenogram showing widening at the aortic area and fluid in the right side of the chest

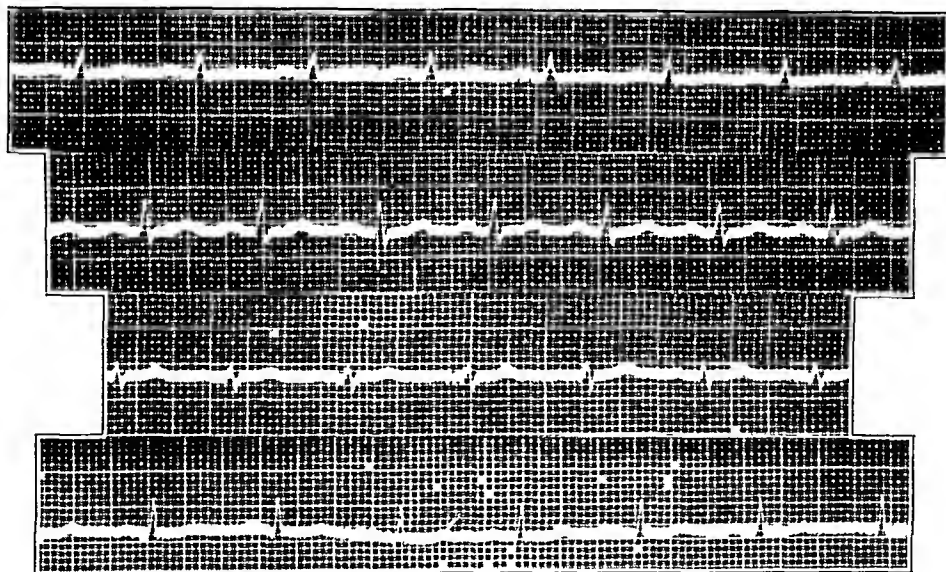


Fig 7 (case 2) —Electrocardiogram taken with the patient reclining in bed (resistance, 400 ohms, auricular rate, 100, ventricular rate, 100, PR interval, 0.2 second, rhythm, regular)

marked amount of calcification. Between the other cusps the commissures were widened. The orifices of the coronary arteries appeared to be normal. In the ascending portion of the aorta on the posterior surface there was a large aneurysm filled with a clot. From this aneurysm there were a few outward pocketings. Two small openings were disclosed near the origin of the superior vena cava, where it had been perforated by the aneurysm. Below this the superior vena cava was constricted because of the pressure of the aneurysm. Anteriorly the bifurcation of the trachea seemed to be compressed.

About 2,000 cc of serosanguineous fluid, containing a large amount of fibrin was present in the right pleural cavity. The right lung weighed 350 Gm and was atelectatic. The left lung weighed 350 Gm and had a thickened pleura. Surfaces made by cutting showed congestion and were reddish gray.

The abdominal viscera were normal except for passive congestion.

*Anatomic Diagnosis*—The anatomic diagnosis was (1) syphilitic aortitis, (2) a ruptured aneurysm of the ascending aorta, (3) a fistula involving the aorta and

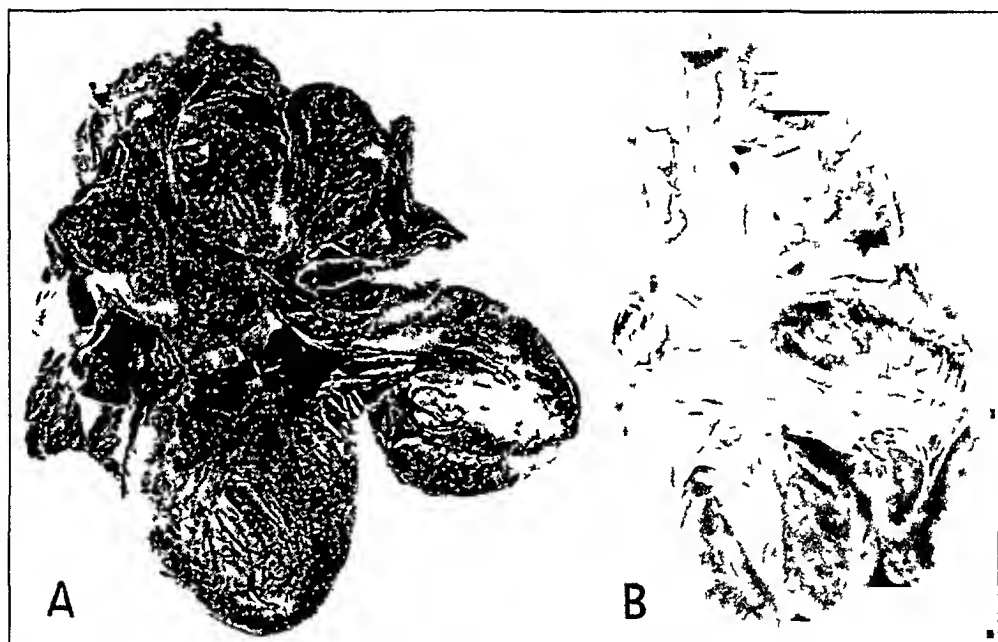


Fig 8 (case 2)—A, the heart is opened on the aortic side, showing the aneurysm with two small openings. B, the heart is opened on the side of the vena cava, showing two small communications near the origin of the cava.

vena cava, (4) acute congestive heart failure, (5) chronic rheumatic endocarditis and (6) pulmonary atelectasis, with pleural effusion.

#### COMMENT

Pepper and Griffith, in 1890, called attention to four principal diagnostic signs and symptoms. These are

- 1 Cyanosis, edema, coldness and distention of the veins of the upper part of the body, with other evidence of obstruction of the circulation of blood in the tributaries of the superior vena cava. They stated that these signs may appear over all the body above the waist line or may be limited to certain parts. The face and neck are almost invariably

affected, but the arms, shoulders and thorax may or may not be involved. Sometimes the changes are unilateral. These variations depend on the location of the perforation in the vena cava, that is, whether it is above or below the azygos vein, and the extent of the compression of the vena cava by the aneurysm. The cyanosis is the result of the impeded venous return, consequent to pressure on and within the vena cava, rather than the result of mixture of arterial and venous blood. Dyspnea may be due to compression of the trachea by the aneurysmal mass, to edema of the larynx or lungs or to hydrothorax.

2 Suddenness of onset of symptoms. The onset of symptoms has taken place under various states of rest and activity but has been sudden in 62 per cent of the cases.

3 Evidence from physical examination of tumor in the thorax and the probability that it is aneurysmal. Roentgenographic examination confirms the diagnosis in many cases.

4 Existence of a murmur characteristic of a communication between an artery and a vein. The murmur was first described, by Dr James Hope,<sup>1</sup> as a "continuous murmur augmented in intensity during the ventricular systole and diastole and in both attended with a great degree of purring tremor." Thurnam,<sup>2</sup> in 1840, described the murmur as a "superficial, harsh, and peculiarly intense swaying or blowing sound accompanied by an equally marked purring tremor, heard over the varicose orifice, and in the current of circulation beyond it, this sound is continuous, but is loudest during the systole, less loud during the diastole, and still less so during the interval."

In addition to these four diagnostic criteria of Pepper and Griffith, Klinck (1936) mentioned the hepatic pulsation which had been observed by Hoover and Beams<sup>3</sup> in several cases of fistula between the femoral artery and the vein, as well as in cases of a communication between the carotid and the jugular vein. That a pulsating liver may be found in some cases of fistula involving the aorta and the vena cava is not doubted, although it is strange that this has previously been overlooked. Hoover and Beams stated that the arteriovenous leak alone does not produce the hepatic pulsation until the caval pressure increases as a result of the incompetence of the heart caused by the fistula.

We should like to emphasize the diagnostic importance of pulsation of superficial veins. This was present in both of our cases and was

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1 Hope, James. *A Treatise on the Diseases of the Heart*, ed 3, London, J Churchill, 1839, quoted by T Shennan (1925).

2 Thurnam, cited by T Shennan (1925).

3 Hoover, C F, and Beams, A J. *The Diagnosis and Pathologic Physiology of Arteriovenous Aneurysms*, Arch Int Med 33 1 (Jan) 1924.

responsible for the making of the correct diagnosis. Pulsation of veins was mentioned in only 10 other cases, but we believe that it probably occurred more often.

Another interesting observation was the presence of the sign of Hall and Rowlands. Leonard Hill,<sup>4</sup> working with Rowlands and others, reported in 1912 on his observations with blood pressure readings for the arms and legs. He noted that normal persons in a reclining position had no marked change in blood pressure in the arms and legs. In cases of aortic regurgitation, however, the pressure in the legs was increased over that in the arms. In 1923 Lewis and Drury<sup>5</sup> showed clinically in 5 cases of arteriovenous aneurysm resulting from war injuries and experimentally after operations on dogs that arteriovenous aneurysm or side to side anastomosis resulted in a lowering of the diastolic pressure, a water hammer pulse, an increase in the blood pressure in the leg over that in the arm (Hall and Rowlands sign of differential blood pressure in the arm and leg), capillary pulsation, increased cardiac rate and other manifestations—the hydrodynamic phenomena of aortic regurgitation. This was true in 1 of our cases in which the blood pressure had been recorded for both legs and arms.

The condition must be differentiated from other obstructions of the superior vena cava. Cases of obstruction due to compression and thrombosis are at times almost impossible to differentiate from cases of arteriovenous fistula. The severe edema and cyanosis, limited sharply to the upper part of the body, seem to be more or less characteristic of fistula, whereas the alterations may not be so extreme with other obstructions, because the conditions are more favorable for the formation of collateral circulation. The characteristic murmur is a helpful sign. It has been reported in cases of obstruction, but in the presence of this finding there is much more likely to be a fistula. The systolic pulsation of the veins is probably the most accurate sign of a varicose aneurysm, it has been absent more often than present. Signs of aortic regurgitation, with the blood pressure in the leg greater than that in the arm, are suggestive.

#### SUMMARY

- 1 A review of the literature and the history and findings in 2 cases of fistula involving the aorta and vena cava are presented.
- 2 The diagnostic criteria are discussed.
- 3 The presence of pulsating superficial veins is emphasized as it establishes the diagnosis.

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5 Lewis, T., and Drury, A. N. Observations Relating to Arteriovenous Aneurysm, *Heart* **10** 301 (Oct.) 1923.

4 The presence of the sign of Hall and Rowlands (an increase in the blood pressure in the leg over that in the arm) is noted as a suggestive aid in the diagnosis of arteriovenous fistula

Dr Newton Evans, Chief of the Department of Pathology, gave us permission to use the autopsy material, William F Davis supplied the photographs, and Mrs Ella Moyers and Esther Young helped collect the material for the bibliography

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# BUNDLE BRANCH BLOCK

CRITERIA OF CLASSIFICATION, DIAGNOSIS AND PROGNOSIS, A STUDY  
OF TWO HUNDRED AND TEN CASES, WITH FOLLOW-UP DATA

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DETROIT

Since Eppinger and Rothberger, in 1910, reported their experimental work on dogs in which the right and left branches of the His bundle were severed, a large volume of literature on this subject has accumulated. In recent years several workers have analyzed case records in an effort to determine what if any are the prognostic implications of electrocardiographic evidence of bundle branch block. Among the more recent of these surveys have been those of Willius,<sup>1</sup> King,<sup>2</sup> Wood,<sup>3</sup> Graybiel and Sprague<sup>4</sup> and Sampson and Nagle.<sup>5</sup> In 1934 Wilson and his co-workers,<sup>6</sup> experimenting with serial precordial leads for human beings and with curves obtained after section of the right bundle branch in dogs, were able to show that certain electrocardiographic patterns, previously not fully understood, represented right bundle branch block in man. These workers<sup>7</sup> described "electrocardiograms of an unusual type" which also were thought to be representative of right bundle branch block. Shortly afterward Bayley,<sup>8</sup> using Wilson's criteria for the diagnosis of right bundle branch block, subdivided all his cases into four groups, the basis of the subdivision being variations in the configuration of the QRS complex.

If Wilson's conclusions are accepted, the diagnosis of bundle branch block will be made more frequently than has been done in the past

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Furthermore, with the inclusion of more cases in this group, especially those of a type previously not included, it might become more imperative to alter somewhat the usual opinion with regard to the prognosis when this lesion is present

#### SELECTION OF CASES

We have reviewed all the cardiograms taken at Harper Hospital and in the private practice of one of us over a ten year period (1927 to 1936) along with the case records. The curves have been reread in the light of the newer criteria. In 179 (85.2 per cent) of the 210 cases of bundle branch block in this series, follow-up information has been obtained. In 64.4 per cent of these cases the patient was seen in private practice, the remainder (35.4 per cent) were semicharity or charity patients. Only 17.7 per cent were outpatients, the others were hospitalized.

#### CLASSIFICATION

Our cases of bundle branch block have been divided into four main groups. In group 1 were included all those believed to be cases of complete left bundle branch block. We have differentiated between heterophasic and homophasic left bundle branch block, as suggested by Graybiel and Sprague.<sup>4</sup> Heterophasic left bundle branch block (group 1a) is represented by the classic "levogram." All the tracings for this group of cases had a QRS interval of 0.12 second or more. The QRS complex was frequently notched, the T wave was exaggerated and pointed in a direction opposite to the main deflection of the QRS complex and, finally, the main deflection of the QRS complex was directed upward in lead I and downward in lead III (fig 1). Eighty cases fell into this group. In the cases in group 1b, cases of homophasic left bundle branch block, the tracing differed from the heterophasic type only in that the T wave was directed upward in lead I and downward in lead III. We had 10 such cases (fig 2).

Group 2 included cases of complete right bundle branch block. Its subdivisions were patterned after Bayley's<sup>8</sup> scheme. In the cases in group 2a there was the classic "dextrogram" (fig 3). "In lead I the chief initial deflection is a broad downward excursion, S, which is preceded by a smaller upward movement, R. T<sub>1</sub> is upright. In lead III, the chief initial deflection is a broad, notched, upward excursion, R which is preceded by a smaller dip, Q. T<sub>3</sub> is inverted." The QRS interval in every instance was 0.12 second or more. Fourteen of our cases belonged in this group.

Eighteen cases were placed in group 2b (fig 4). The tracings in these cases differed from those in the preceding group of cases only in that R in lead I had a greater amplitude than S.

Group 2c included 21 cases (fig 5). Lead I of the tracings in this group of cases resembled lead I in the tracings in the cases in group 2b; however, in lead III the most conspicuous QRS deflection was a narrow inverted spike followed by a broad upright summit.

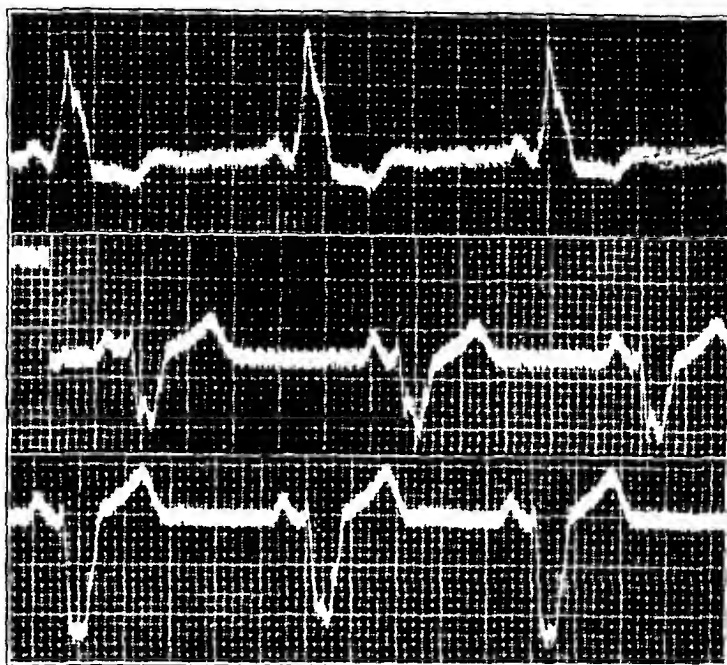


Fig 1—Left bundle branch block, heterophasic, of type 1a The QRS interval, 0.16 second, is notched and slurred in all leads The T wave is prominent and opposite to the main deflection of the QRS complex The main deflection of QRS is directed upward in lead I and downward in lead III

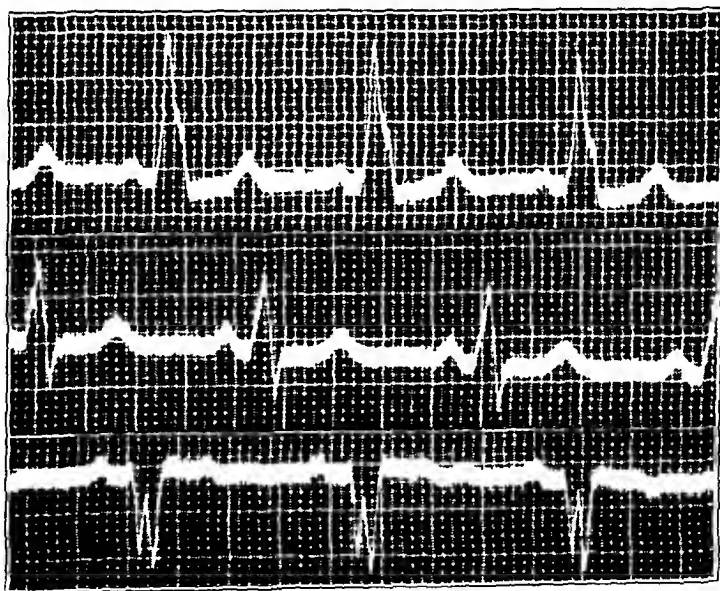


Fig 2—Left bundle branch block, homophasic, of type 1b The QRS interval, 0.14 second, is notched and slurred in all leads The main deflection of QRS is directed upward in lead I and downward in lead III The T wave is in the same direction as the main deflection of QRS

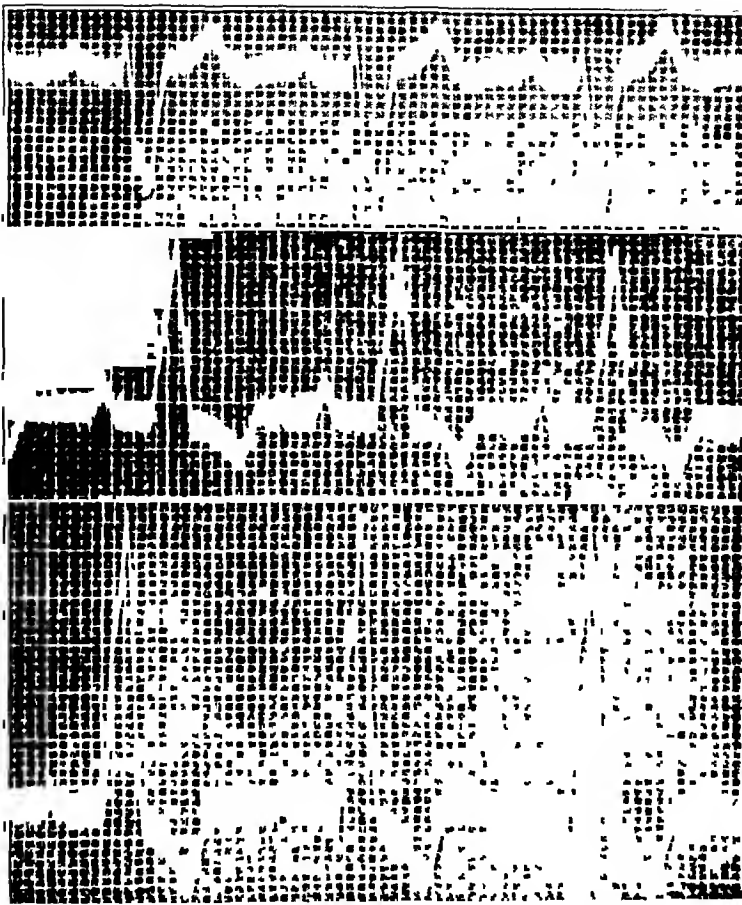


Fig 3—Right bundle branch block of type 2a The QRS interval, 0.15 second, is notched and slurred in the first two leads and slurred in lead III The T wave is prominent and points in a direction opposite to the main deflection of QRS The main deflection of QRS is directed downward in lead I and upward in lead III In lead I the chief initial deflection is a broad downward excursion, S, which is preceded by a smaller upward movement, R In lead III the chief initial deflection is a broad upward excursion, R, which is preceded by a smaller dip, Q

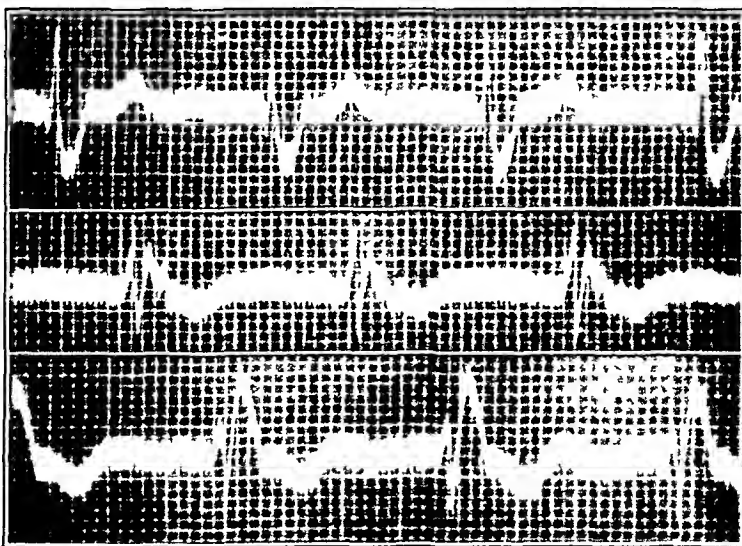


Fig 4—Right bundle branch block of type 2b The QRS interval, 0.16 second, is notched and slurred in all leads In lead I there is a broad downward excursion, S, which is preceded by a steep upward spike The amplitude of R in lead I is greater than that of S In lead III the main deflection of QRS is directed upward The T wave is in a direction opposite to the main deflection of QRS

In the 6 cases in group 2d the tracing differed from that in the previous group of cases only in that it lacked the broad upward summit in lead III (fig 6). It will be noted that two features were common to all four types of right bundle branch block, namely, a QRS interval of 0.12 second or more and a deep, broad downward deflection, S, in lead I.

Group 2e was reserved for those cases in which the curves were similar to those described by Wilson<sup>7</sup> as "electrocardiograms of an unusual type" and said by him to represent right bundle branch block (fig 7). In these curves the amplitude of all the deflections in lead I was small, there was a conspicuous S deflection and T was flat or upright. Leads II and III resembled those seen in cases of left bundle

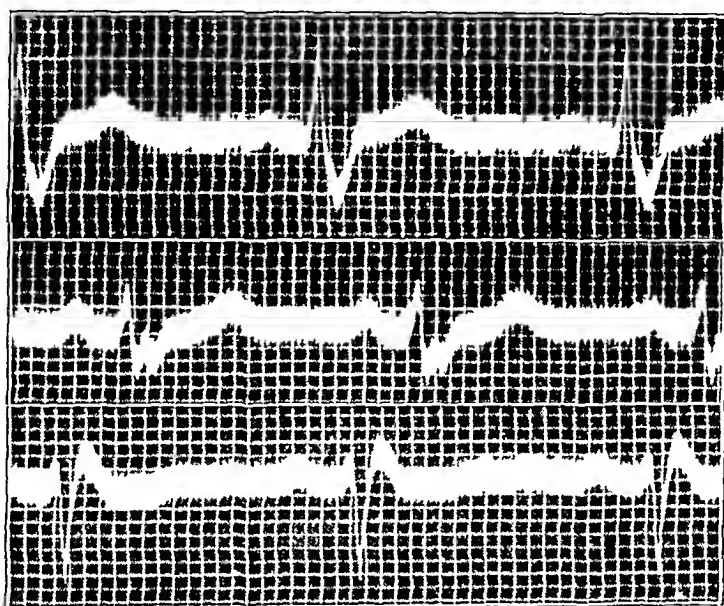


Fig 5—Right bundle branch block of type 2c. The QRS interval, 0.15 second, is notched in lead II and slurred in all leads. In lead I there is a broad downward excursion, S, preceded by a sharp spike, R. The amplitude of R is greater than that of S. In lead III the most conspicuous QRS deflection is a narrow inverted spike followed by a broad upward summit.

branch block. Wilson stated that this type of curve is probably not common but that its frequency is not known. In our series, 3 cases were found in which this type of tracing was obtained. A fourth curve showing similar characteristics was discovered as a terminal feature in a case which had previously belonged in group 4.

Group 3 consisted of 7 cases in which the disorder was difficult to classify. In all the cases the QRS interval was 0.12 second or more. In most of these cases there were all the criteria necessary for the diagnosis of bundle branch block, but localization characteristics were lacking. For example, figure 8 exhibits the curve in a case in which QRS was similarly directed in leads I and III.

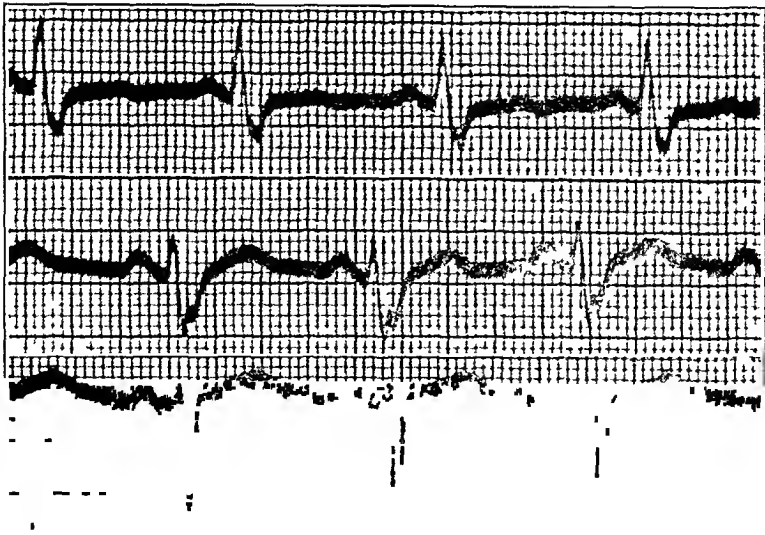


Fig 6—Right bundle branch block of type 2 d The QRS interval, 0.14 second, is notched and slurred in the first two leads In lead I there is a deep, broad downward deflection, S, preceded by an upward spike, R In lead III the main deflection of QRS is directed downward and is not followed by an upright summit

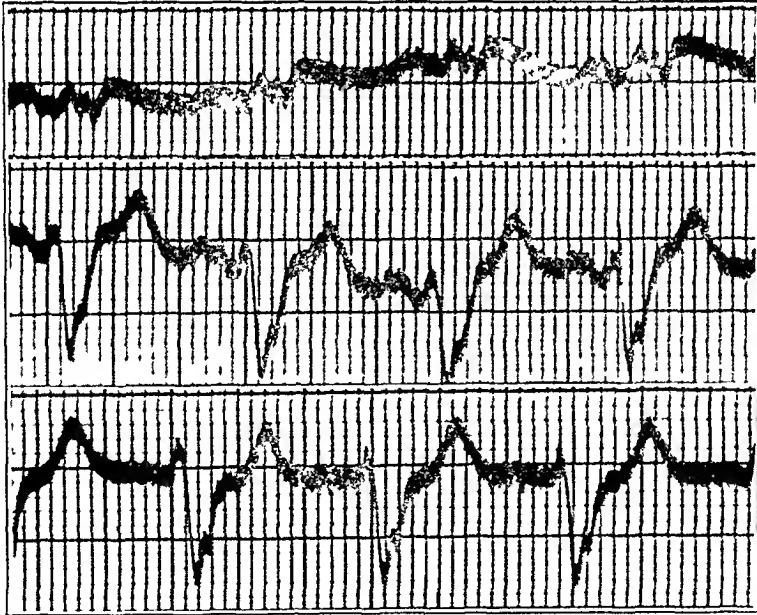


Fig 7—Right bundle branch block of type 2 e The QRS interval, 0.16 second, is notched in all leads In lead I the amplitude of all deflections is small, there is a conspicuous S deflection and T is flat or upright The tracings in leads II and III resemble those seen in cases of left bundle branch block



Group 4 consisted of cases in which the curves exhibited intra-ventricular conduction defects. There were included all the curves conforming to the type first described by Oppenheimer and Rothschild<sup>9</sup> as representative of arborization block. As such they were characterized by a QRS interval exceeding 0.1 second, notching of the R wave, low voltage in all three leads and absence of the typical diphasic curve with a huge T wave found in cases of bundle branch block (fig. 9). In this last group were included cases in which there were other curves in which the QRS interval exceeded 0.12 second but which lacked the distinguishing features of any of the previously described types. Fifty fell into this group of cases of heterogeneous type.

The ratio of the incidence of left bundle branch block to right bundle branch block was 90 to 63. This is comparable to the 103 to

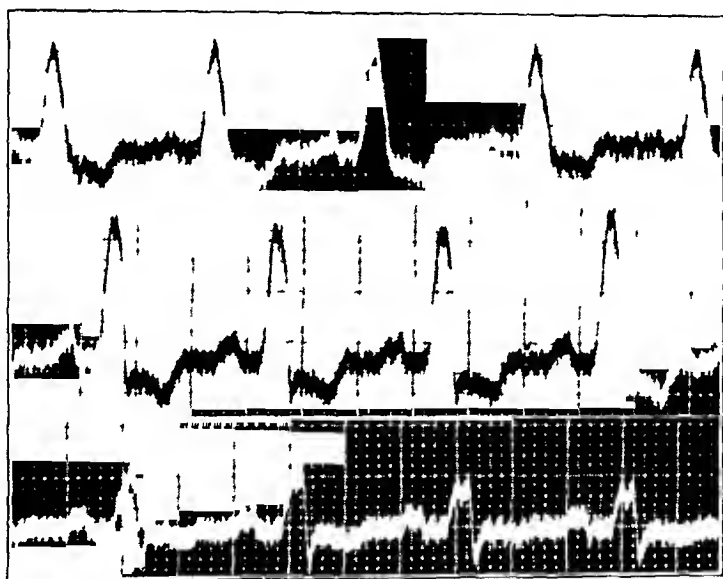


Fig. 8—Bundle branch block of indefinite localization. The QRS interval, 0.13 second, is notched in leads II and III. The main deflection of QRS is directed upward in all three leads.

70 ratio in Bayley's<sup>8</sup> series and represents a higher incidence of right bundle branch block than that reported by other investigators. Graybiel and Sprague<sup>4</sup> found 125 cases of left bundle branch block as compared with 29 cases of right bundle branch block.

#### DISTRIBUTION

*Sex*—There were 126 (60 per cent) males and 84 (40 per cent) females.

*Race*—All but 5 (3 Negroes, 1 Filipino and 1 Japanese) of the total number of patients were of the white race.

<sup>9</sup> Oppenheimer, B. S., and Rothschild, M. A. Electrocardiographic Changes with Myocardial Involvement, *J. A. M. A.* 69:429, 1917.

*Age*—The largest number of cases occurred in patients in the sixth and seventh decades. The youngest patient was  $4\frac{1}{2}$  years old and the oldest 82. Table 1 shows the age distribution for the various groups.

*Etiology*—No attempt was made to separate the arteriosclerotic from the hypertensive patients, together they accounted for 76.6 per cent of all the patients. Rheumatic heart disease was the probable cause in 9.5 per cent. The highest percentage of rheumatic and congenital heart disease occurred in the cases in group 2 (right bundle branch block). Table 1 shows the distribution of cases with respect to the chief etiologic factors.

#### ASSOCIATED FINDINGS

*General Condition of the Patient*—In 202 of the 210 cases there was sufficient information in the record to permit approximate evalua-

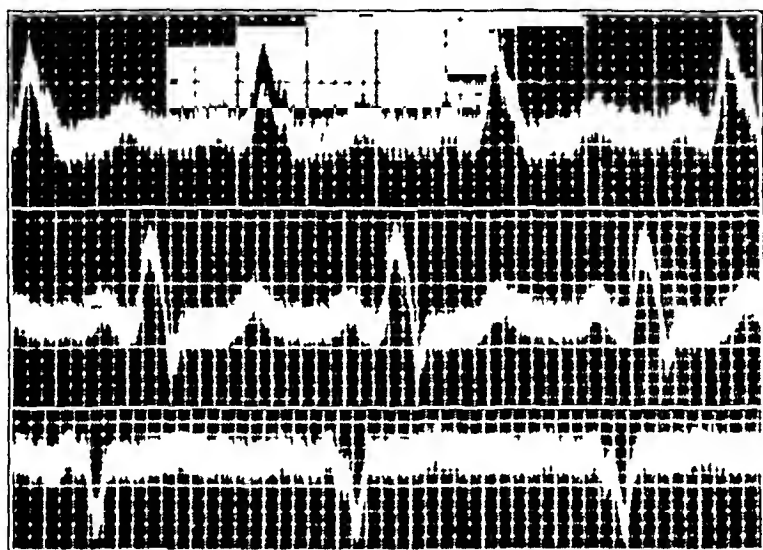


Fig 9—An intraventricular conduction defect of lesser degree (type 4). The QRS interval, 0.14 second, is notched and slurred in all leads. There is low voltage in all three leads. The T wave is conspicuous, and the deflection is not opposite to that of QRS.

tion of the patient's general condition at the time the diagnosis of bundle branch block was made. In 64 cases (31.6 per cent) the condition was considered good, that is, there was no evidence clinically of any cardiac embarrassment or any history of previous cardiac decompensation. In 83 cases (41 per cent) the patients were regarded as having been in fair condition, having shown symptoms relative to their cardiovascular system or signs of limited cardiac reserve but no evidence or only slight evidence of cardiac failure. In 55 cases (27.2 per cent) the patients presented definite evidence of cardiac failure when first seen, these were classified as being in poor condition. Twenty-one were in a terminal condition when brought into the hospital and were dead within a few days.

*Valvular Disease*—In 32 cases a diagnosis of valvular heart disease was made. Twelve were mitral lesions, 11 were aortic, 6 were combined aortic and mitral and 3 were congenital.

*Associated Arrhythmias*—The most frequently encountered arrhythmia in patients with bundle branch block is auricular fibrillation. It occurred in 29 cases (13.8 per cent). It appears to be proportionately

TABLE 1—*Distribution of Cases*

		Group 1	Group 2	Group 3	Group 4	Total
Age	0-9	0	1	0	0	1
	10-19	0	3	0	2	5
	20-29	2	3	0	0	5
	30-39	2	1	2	7	12
	40-49	12	10	2	11	35
	50-59	25	13	2	11	51
	60-69	31	20	0	13	64
	70-79	13	10	1	5	29
	80-89	2	1	0	1	4
Sex	Male	48	38	5	35	126
	Female	42	25	2	15	84
Etiologic factors	Arteriosclerosis	68	47	6	40	161
	Rheumatic fever	8	7	0	5	20
	Syphilis	5	1	1	2	9
	Thyroid disorder	6	1	0	1	8
	Congenital condition	0	3	0	0	3
	Miscellaneous conditions	1	2	0	2	5

TABLE 2—*Associated Data*\*

	Group 1	Group 2	Group 3	Group 4	Total	Percentage
Number of cases	90	63	7	50	210	
Cardiac enlargement	71	40	6	33	150	74.0
Cardiac failure	65	23	2	27	117	57.0
Previous history of heart disease	61	28	2	26	117	53.0
Bedridden	28	15	1	17	61	29.1
Ambulatory	52	40	6	31	129	61.7
Partially bedridden	10	7	0	2	19	9.0
Coronary thrombosis	15	8	1	7	31	15.0
Reduplication of apical second sound	2	0	0	0	2	1.0
Gallop rhythm	8	3	0	8	19	9.2
Angina	21	9	1	8	39	18.9
Distant heart sounds	36	14	4	20	74	35.9
Auriculoventricular delay	11	10	1	3	25	11.9
Auriculoventricular dissociation	6	2	1	2	11	5.2
Auricular fibrillation	12	8	0	9	29	13.8

\* Some of the records were not complete in every respect. When information was lacking on a particular point, that case was not included in the totals and percentages. This will explain certain apparent mathematical discrepancies in this table.

distributed among the four major types of bundle branch block. Auriculoventricular delay, as evidenced by prolongation of the PR interval beyond 0.2 second, was noted in 25 cases (11.9 per cent). Auriculoventricular dissociation occurred in 11 cases (5.2 per cent). Gallop rhythm was detected in 19 cases (9.2 per cent), but this was probably not always carefully searched for. Other arrhythmias present were ventricular tachycardia, 3 cases, paroxysmal auricular tachycardia, 2 cases, auricular flutter, 3 cases, and pulsus alternans, 2 cases.

*Previous History of Heart Disease*—It is surprising how many patients with bundle branch block give no history referable to the heart. In this series 58 per cent of the patients had had cardiac symptoms. However, many of these had noted merely dyspnea on exertion or had a minor complaint not at all incompatible with their age. Angina pectoris was reported by 18 per cent. Many patients of the entire group did not show cardiac symptoms until some terminal situation arose.

*Cardiac Enlargement*—The heart was found to be enlarged to percussion in 155 cases (74 per cent), this was confirmed by roentgen examination in 66 cases. In the remaining 26 per cent the heart was not significantly enlarged.

*Cardiac Failure*—In 117 cases (55.5 per cent) there were either physical signs of cardiac decompensation or else a history of previous decompensation. In many of these cases the evidences of cardiac insufficiency were minimal.

*Coronary Thrombosis*—In 31 cases there had been an attack of acute coronary occlusion, or there was a previous history of coronary thrombosis. It was evident that the two conditions were present at the time that the bundle branch block was first discovered. In most cases it was impossible to tell whether the bundle branch block had previously existed or whether it was a direct result of the recent coronary accident for which the patient had been brought to the hospital. It was felt that in some of these cases the two conditions might have appeared simultaneously, the thrombus being so situated as to interfere with the blood supply to the bundle branch. The total of 31 cases in this group does not include the cases in which the patients ultimately died of coronary thrombosis without having shown evidence of occlusion when the bundle branch block was discovered.

The majority of the patients were ambulatory (61.7 per cent) when the bundle branch block was first discovered, 9 per cent were partially confined to bed and 29.1 per cent were confined to bed. Many of the latter group, however, conceivably had had the lesion for some time prior to its discovery. In general, it may be said that bundle branch block does not of necessity, nor does it usually imply that the patient will be confined to bed because of it.

#### PROGNOSIS

A conclusion with regard to the prognosis in bundle branch block cannot be sharply drawn. In most cases it was impossible to be certain how long the lesion had been present before it was discovered. Figures will vary depending on whether electrocardiograms are taken as a routine measure or whether they are taken only in cases of suspected heart disease. At most one can merely determine the duration of life

after the discovery of the lesion. Notwithstanding the number of variables and extraneous factors, if a large number of patients with this lesion are studied, certain facts are revealed with regard to prognosis which may approximate the truth.

Of the 210 patients with proved bundle branch block and intra-ventricular block seen in a ten year period, 123 (68.8 per cent) were dead, 56 (31.2 per cent) were living and 31 could not be traced (table 3). For those who died, the average length of life after the discovery of the lesion was 0.93 years. The 56 patients who were still alive had been living for an average of 3.36 years since the discovery of bundle branch block. These figures indicate a slightly graver prognosis than that reported by previous investigators<sup>10</sup>. The duration of life in the

TABLE 3—*Duration of Life in Cases of Bundle Branch Block*

	Number of Cases	Number Dead	Number Living	Number Lost	Percentage Living	Average Length of Life After Discovery of Lesion of Those	
						Who Have Died, Yr	Still Alive, Yr
Group 1	90	53	20	12	25.6	1.11	3.35
a	80	54	15	11	21.7	0.97	2.90
b	10	4	5	1	55.5	3.00	4.70
Group 2	63	32	19	12	37.2	1.14	3.65
a	14	8	4	2	38.8	0.89	4.04
b	18	8	6	4	42.8	1.05	4.35
c	22	11	6	5	35.2	1.90	2.37
d	6	2	3	1	60.0	0.03	4.30
e	3	3	0	0	0	0.02	
Group 3	7	3	2	2	40.0	0.12	6.45
Group 4	50	30	15	5	33.3	0.45	2.65
Total	210	123	56	31	31.2	0.93	3.36

cases in groups 1 and 2—typical left bundle branch block and typical right bundle branch block, respectively—was approximately the same as that reported for other series, it was slightly over 13 months for both groups.

In the cases in group 1b (the homophasic left bundle branch block of Graybiel and Sprague<sup>4</sup>) there was the best life expectancy for any of the groups. Of the 10 cases in this group, 4 were fatal after an average period of three years, in 5 cases the patient was living after an average period of 4.7 years. These figures are relatively so much higher than the figures for the group of cases of heterophasic type that one may be led to suspect that these curves may represent only partial bundle branch block.

The duration of life in the cases in groups 2a and 2b does not vary markedly from the averages for the entire series. Of the 22 cases in group 2c, 11 were fatal, the patient having survived for an average of

<sup>10</sup> Willhus<sup>1</sup> King<sup>2</sup> Wood, Jeffers and Wolferth<sup>3</sup>

19 years after the diagnosis of bundle branch block was made. This is almost twice as long as the survival period in cases of any of the other types of right bundle branch block. In group 2d there were not enough cases for comparison with other groups. Group 2e consisted of 3 cases in which the curves were similar to those described by Wilson<sup>7</sup> as "electrocardiograms of an unusual type in right bundle branch block." In all 3 of our cases the patient was definitely in a terminal condition when the electrocardiogram was taken, and no previous curves had been made. These patients lived 1, 4 and 20 days, respectively. A fourth patient whose curve conformed to this pattern was seen just before death, previously there had been type 4 bundle branch block. One of Wilson's 3 patients was dead 9 days after the lesion was detected. No statement was made by Wilson with reference to the 2 other patients.

For group 4, which included cases of minor degrees of bundle block and intraventricular block, there was the worst prognosis of all. In 30 of the 50 cases death occurred after an average of 0.45 year. This is perhaps explained by the fact that in a good share of these cases the patient was in a terminal condition when admitted to the hospital. The terminal electrocardiographic picture for patients who have previously had conduction defects of various kinds shows simply a widened QRS interval and low voltage. In that respect it resembles the others in this group of cases. The inclusion of patients who were moribund tends to indicate a graver prognosis than is warranted. In 15 of the cases in group 4 the patients who are still living have survived an average of 2.65 years.

Notwithstanding the fact that for our patients with bundle branch block who have died the average duration of life has been approximately 1 year, many have lived much longer. Thirty have lived more than 4 years after the lesion was detected. Of these, 22 are still living, 2 having passed their eighth year, 6 their seventh year and 6 their sixth year.

We have made an attempt to analyze the influence of certain factors on the prognosis in cases of bundle branch block. The results are recorded in table 4. It will be noted that the factor of age does not play a constant role. In the groups of very young patients there was a higher percentage of patients still living than in the groups of older patients. For the patients from 60 to 69 years of age (the largest group) the average length of life in fatal cases was greater than that for any other age period. While it is dangerous to generalize, our figures indicate that older patients with bundle branch block do better than young patients with the same condition. Age, in and of itself, does not render the prognosis more grave.

The 3 patients with bundle branch block accompanied by a congenital cardiac lesion apparently enjoyed the best life expectancy of the entire group, however, 3 cases are not enough to permit of comparison. Patients with lesions occurring in the presence of syphilitic heart disease had a poor prognosis, while patients in whom bundle branch block was secondary to thyroid heart disease had a better life expectancy than

TABLE 4—*Factors Influencing Prognosis in Bundle Branch Block*

	All Cases	Num ber of Cases	Num ber Dead	Num ber Living	Living, %	Num ber Not Traced	Average Duration of Life After Discovery of Lesion in Those Now Dead, Yr
All cases		210	123	55	30.8	32	0.93
Age							
0-9		1	0	1	100.0	0	
10-19		5	2	2	50.0	1	1.04
20-29		5	2	3	60.0	0	0.10
30-39		12	8	3	27.2	1	0.64
40-49		35	24	9	27.5	2	0.50
50-59		51	28	15	34.8	8	0.65
60-69		64	36	16	30.7	12	1.44
70-79		29	17	5	22.7	7	0.86
80-89		4	3	1	25.0	0	0.66
Etiologic factors							
Arteriosclerosis		161	94	39	29.3	28	0.91
Rheumatic fever		20	14	6	30.0	0	0.80
Syphilis		9	7	2	22.2	0	0.17
Thyroid disorder		8	3	4	57.1	1	1.77
Congenital condition		3	1	1	50.0	1	2.08
Miscellaneous conditions		5	3	0	0	2	0.00+
Sex							
Male		126	81	32	28.3	18	0.83
Female		84	42	24	36.3	16	1.08
Economic status							
Private patients		134	80	33	29.2	21	0.94
Charity patients		75	42	23	35.3	10	0.89
General condition							
Good		64	23	25	52.0	16	1.76
Fair		83	49	25	34.2	9	1.15
Poor		55	49	2	3.9	4	0.81
Cardiac enlargement		154	99	33	25.0	23	0.91
No cardiac enlargement		38	16	13	44.8	9	1.29
No previous history of heart disease		88	43	31	41.6	14	1.08
Previous history of heart disease		116	77	22	22.2	17	0.87
QRS of 0.15 sec. or longer		53	38	11	17.1	4	0.87
Delayed auriculoventricular conduction		25	20	5	20.0	0	0.83
Auricular fibrillation		29	20	6	23.0	3	0.83
Gallop rhythm		19	16	2	11.1	1	0.48
Coronary thrombosis		31	24	4	14.2	3	43.5 days

the rest of the patients. The duration of life in cases of arteriosclerotic heart disease plus bundle branch block was similar to the average duration of life in all the cases in the series. When the lesion occurred as a result of rheumatic heart disease, the duration of life was slightly less than that for the entire group.

Females tolerated the lesion better than did males. Private patients fared better than ward and dispensary patients. The general condition of the patient appeared to be an intangible factor in the prognosis.

For those whose condition was deemed poor at the time when bundle branch block was discovered, the outlook was grave, indeed, as the table shows

The presence of other arrhythmias in association with bundle branch block indicated, in general, a lessened life expectancy. The finding of gallop rhythm, in particular, predicted an unfavorable prognosis.

For those patients who had suffered coronary thrombosis or in whom a bundle lesion was noted after acute coronary occlusion the prognosis was poor.

Of the 123 patients who have died, 60 have died of cardiac failure, 29 of coronary thrombosis, 2 of subacute bacterial endocarditis, 2 during an Adams-Stokes attack and 26 of noncardiac conditions, in 4 cases the cause of death was not known.

*Successive Electrocardiograms*—In 58 cases electrocardiograms were secured after an interval of several months to several years following the taking of the curves which first revealed the bundle branch block. In a number of instances we were able to follow the cases electrocardiographically at regular intervals over a relatively long period. In 18 cases the curves remained unchanged throughout the entire period of observation. In 16 cases they showed progression in the severity of the lesion. In 11 cases there was graphic evidence of improvement. In the remaining 13 cases there were changes which we were unable to interpret as indicating either improvement or regression. In 16 cases changes were noted in the configuration of the QRS complex of sufficient magnitude to warrant concluding that the original lesion had been altered or had been overshadowed by another one. Left bundle branch block was succeeded by right bundle branch block in a few instances and vice versa. Type 4 bundle branch block was not an uncommon terminal finding in cases of previous typical complete bundle branch block. There were also infrequent changes from one to any of the other subgroups of right bundle branch block (Bayley). Changes from one type of bundle branch block to another were frequently seen just before death; these may have been due to superimposed lesions which were the causes of death, respectively, or else they were manifestations of deranged conduction in a completely failing myocardium.

*Transient Bundle Branch Block*—Herrmann and Ashman,<sup>11</sup> in 1931, reviewed all the previously reported cases of transient bundle branch block (10 in all) and added 8 cases of their own. Morris and McGuire<sup>12</sup> reported 2 cases of transient complete bundle branch block which came on acutely in association with acute circulatory failure. Hamburger<sup>13</sup> described a case of transient bundle branch block from digitalis in a

11 Herrmann G. and Ashman, R. Am Heart J 6:375, 1931

12 Morris, R. S. and McGuire, I. Am J M Sc 184:202, 1932

13 Hamburger, W. W. M Clin North America 13:177, 1926



case of advanced congestive heart failure Willius and Anderson<sup>14</sup> concluded that "transient complete bundle branch block is not a rare condition" In our own series there were 9 cases of transient bundle branch block In 4 of these cases the disorder cleared up after a course of rest in bed and digitalization, indicating that cardiac failure was probably the basis for the disturbance in conduction However, in 3 of these cases there were recurrences of the bundle branch block during subsequent cardiac breakdowns In 2 of the 9 cases evidence of bundle branch block developed simultaneously with the occurrence of coronary occlusion As recovery from the coronary occlusion took place, the bundle branch block disappeared as well In 1 case bundle branch block occurred during an attack of appendicitis and cleared up subsequent to appendectomy In another case recovery apparently followed thyroidectomy In the ninth case the disappearance of bundle branch block was spontaneous

#### COMMENT AND SUMMARY

The entire series of electrocardiograms taken at Harper Hospital over a ten year period were reviewed Two hundred and ten cases of bundle branch block and intraventricular block were found In 179 cases (85.2 per cent) the subsequent course was studied, in the remainder of the cases the patient could not be followed Using Wilson's criteria for the diagnosis of right bundle branch block, we were able to confirm his observation that that condition is more frequent than was previously supposed The ratio of males to females in our series was 3 to 2 The largest number of cases occurred in patients in the sixth and seventh decades About three fourths of the cases occurred in conjunction with arteriosclerotic heart disease In 15 per cent of the cases there was evidence of frank coronary occlusion

Patients for whom the diagnosis of bundle branch block is made come to the hospital for a variety of reasons The diagnosis is practically never made or even suspected until disclosed by electrocardiographic evidence Consequently, these patients first present themselves with a previous history ranging from good health to complete disability Frequently evidence of bundle branch block is discovered in the electrocardiogram of a patient who has no other signs of cardiac disease In such cases signs or symptoms of cardiac disease may never develop On the other hand, our records reveal repeated electrocardiograms in cases in which bundle branch lesions suddenly developed and death occurred in a short time

There is no "clinical picture" of bundle branch block Although bundle branch block may be discovered in conjunction with what is to all appearances a normal or near normal heart, it is most frequently associated with some degree of cardiovascular disease Statistics in this

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<sup>14</sup> Willius, F. A., and Anderson, M. J. *Am Heart J* 10: 248, 1934

regard do not show the absolute facts, because the taking of electrocardiograms is not a routine procedure and in many cases the condition is not discovered at its inception

As electrocardiograms are usually not taken except when heart disease is suspected or when the patient's condition is being evaluated with regard to surgical or insurance risk, electrocardiographic files are somewhat overbalanced with records showing some form of cardiac damage. The records, therefore, are not a cross section of the findings for the general population or even for patients in a hospital

In general, it may be said that bundle branch block is most frequently found in conjunction with definite heart disease aside from the bundle lesion. Consequently the prognosis in cases of bundle branch block is at best no better than it is in cases of any form of myocardial disease. How much hazard accrues from the bundle branch block is difficult to estimate. In spite of the fact that a majority of the cases occur in aged persons and in patients suffering from cardiac disease, a fair percentage of patients live for a surprising length of time and without great discomfort

The most important factors to be considered in determining the prognosis are the general condition of the patient and the physical signs of cardiac damage. Patients who are in good condition and show little or no signs of cardiac embarrassment are not as a rule in immediate danger. Those who are suffering from other degenerative diseases and present findings of myocardial disease, such as cardiac enlargement, cardiac arrhythmia, dyspnea and peripheral edema, suffer seriously from a bundle branch lesion. Gallop rhythm is an ominous prognostic sign. In cases in which bundle branch block is associated with frank coronary thrombosis the patients are usually destined to early death.

The larger percentage of patients die within the first year after the discovery of the lesion. Those who survive this first year stand an excellent chance of carrying on for a relatively longer time.

Our patients with right bundle branch block lived slightly longer than those with a lesion on the left side. Patients with so-called intra-ventricular block had a poorer life expectancy than those with complete bundle branch block. Our study did not include cases in which there was a minor degree of intra-ventricular block.

The aged patients seemed to withstand the ill effects of bundle branch block as well as did the younger patients.

When bundle branch block was associated with syphilitic heart disease, the prognosis was poor. Patients with bundle branch block secondary to thyroid or congenital heart disease did much better than the average. The rheumatic and arteriosclerotic patients fared about equally well, the prognosis ranking between the two extremes just cited.

Females, in general, lived longer than males with this lesion. Private and charity patients showed no outstanding differences.

# GASTROSCOPIC OBSERVATIONS IN PERNICIOUS ANEMIA

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The close relation between pernicious anemia and changes in the mucosa of the stomach has been well recognized since the time of Austin Flint<sup>1</sup> and Hayem<sup>2</sup>. A brilliant synopsis of all the questions involved has been given by Minot<sup>3</sup>. Friedenwald and Morrison<sup>4</sup> stated as early as 1919 that practically no patient with pernicious anemia is free from gastrointestinal symptoms.

Anatomically there was early general agreement (Faber and Bloch<sup>5</sup>) that the gastric mucosa was thinned or degenerated, that these changes were most pronounced in the cardiac region and that they diminished toward the pylorus. In later times this anatomic concept changed. Cases were described in which the wall of the pyloric region was tremendously thickened by inflammation of the deeper layers, especially of the muscularis propria (Kleemann<sup>6</sup>), and even by the formation of inflammatory polyps—gastritis hypertrophicus polyposa—in the pyloric region (Mayeda<sup>7</sup>). In 1934 M. R. Brown,<sup>8</sup> in a report on the post-

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1 Flint, A. A Clinical Lecture on Anemia, *Am M Times* **1** 181, 1860

2 Hayem, G. Gastrites dégénératives, *Soc méd d hop*, 1896, p 722

3 Minot, G. R. Anemia and the Gastrointestinal Tract. A Synopsis, *Am J Digest Dis & Nutrition* **3** 643, 1936

4 Friedenwald, J., and Morrison, T. Gastro-Intestinal Disturbances in Pernicious Anemia, *J A M A* **73** 407 (Aug 9) 1919

5 Faber, K., and Bloch, C. E. Ueber die pathologischen Veränderungen am Digestionstraktus bei der perniciosen Anämie und über die sogenannte Darmatrophie, *Ztschr f klin Med* **40** 98, 1900

6 Kleemann, A. Ueber die Hypertrophie des Pylorus bei pernicioſer Anämie, *Deutsche Arch f klin Med* **128** 271, 1919

7 Mayeda, T. Ueber die Hypertrophie des Pylorus bei pernicioſer Anämie, *Schweiz med Wchnschr* **51** 699, 1921

8 Brown, M. R. Gastrointestinal Pathology in Pernicious Anemia and Subacute Combined Degeneration of the Spinal Cord, *New England J Med* **210** 473, 1934

mortem examinations in 151 proved cases of pernicious anemia emphasized the frequency of all kinds of gross gastric lesions, not only atrophic gastritis but also benign inflammatory polyps and carcinoma. The gastritis he regularly observed was not only of the atrophic type but also partly of the hypertrophic type. However, he stated that the apparent hypertrophy consisted of interstitial infiltration with leukocytes and replacement of the tubules by fibrous tissue. This description does not agree with the modern definition of hypertrophic gastritis, i. e., not destruction but definite proliferation of tubules accompanied by interstitial infiltration. At any rate, he noted a marked inflammatory process, not merely a degenerative or regressive process. Furthermore, Brown discovered that in 20 cases in which liver therapy had been received no decisive influence was apparent in the histologic picture. Still more important was his observation that the gastritis was most severe near the pylorus. Most of the polyps observed occurred in this region. He also observed enteritis often. These observations seemed to fit in with the theory that inflammatory changes in the pyloric mucosa and the duodenum were the primary cause of pernicious anemia. The so-called pyloric organ, consisting of the Brunner glands of the antrum and the duodenum, is believed to secrete, to a large extent, the "intrinsic factor" (Castle<sup>9</sup>) the absence of which is apparently necessary to cause the entity of pernicious anemia. These observations of Brown therefore agreed closely with the ideas of Faber<sup>10</sup> and Hurst<sup>11</sup> on the importance of primary inflammation of the stomach in the origin of this disease.

It is natural that attempts were made to observe the living gastric mucosa in patients with pernicious anemia by means of the safe flexible gastroscope, which by that time had been invented<sup>12</sup>. This method seemed especially important, since after the routine administration of

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9 Castle, W. B. Observations on the Etiologic Relationship of Achylia Gastrica to Pernicious Anemia. I. Effect of the Administration to Patients with Pernicious Anemia of the Contents of a Normal Human Stomach Recovered After the Ingestion of Beef Muscle, *Am J M Sc* **178** 748, 1929. Castle, W. B., and Townsend, W. C. Observations on the Etiologic Relationship of Achylia Gastrica to Pernicious Anemia. II. Effect of the Administration to Patients with Pernicious Anemia of Beef Muscle After Incubation with Normal Human Gastric Juice, *ibid* **178** 764, 1929. Castle, W. B., Townsend, W. C., and Heath, C. W. Observations on the Etiologic Relationship of Achylia Gastrica to Pernicious Anemia. Nature of the Reaction Between Normal Human Gastric Juice and Beef Muscle Leading to Clinical Improvement and Increased Blood Formation Similar to the Effect of Liver Feeding, *ibid* **180** 305, 1930.

10 Faber, K. Gastritis and Its Consequences, New York, Oxford University Press, 1935.

11 Hurst, A. F. The Unity of Gastric Disorders, *Brit M J* **2** 89, 1933.

12 Schindler, R. Gastroscopy. The Endoscopic Study of Gastric Pathology, Chicago, University of Chicago Press, 1937.

liver therapy (Whipple<sup>13</sup>) autopsy material became rare. Henning,<sup>14</sup> on the basis of his great experience in this field, contended that in each patient with pernicious anemia, diffuse atrophy of the entire gastric mucosa could be observed. Gutzeit and Teitge<sup>15</sup> detected atrophic changes in every patient and said they believed that they never disappeared, in spite of liver therapy, although Teitge observed alterations of pictures, which he said he considered to be due to acute inflammatory attacks. Lehmann,<sup>16</sup> in a monograph published in 1936, reported on 3 cases of pernicious anemia. In the first case he observed in the pale mucosa patches of atrophic gastritis which disappeared almost completely after treatment, the blood vessels that were demonstrable at the first examination disappeared, four small gray patches were the residuum of the foregoing severe atrophic gastritis. The second patient was observed with the gastroscope during a complete remission, only one atrophic patch was seen on the anterior wall. In the third patient, observed during an incomplete remission, only slight diffuse atrophy was seen. In the first 2 cases the improvement of the "tongue of Hunter" equaled that of the changes in the gastric mucosa. Similar cases have been described by Rene Chevallier.<sup>17</sup>

The most important observations were made on 5 patients by Jones, Benedict and Hampton.<sup>18</sup> Their paper presented observations made during remissions and in 3 of these patients also during relapses. In their first patient carcinoma developed. The second patient was studied because of the formation of polyps during a remission, and hypertrophic gastritis was noted, later, however, the mucosa appeared normal gastroscopically. The third patient presented in relapse an atrophic mucosa, which later showed hypertrophic gastritis. The fourth patient was operated on in a remission, and the mucosa appeared red and inflamed and was covered with small "polyps." Four years later the mucosa was practically normal. In the fifth patient they saw that during relapse the mucosa was atrophic and that during a remission it was normal. The authors stated that in each instance no atrophy was present after

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13 Whipple, G. H., and Robschert-Robbins, F. S. Blood Regeneration in Severe Anemia. Standard Basal Ration Bread and Experimental Methods, *Am J Physiol* **72** 395, 1925.

14 Henning, N. *Die Entzündung des Magens*, Leipzig, Johann Ambrosius Barth, 1934.

15 Gutzeit, K., and Teitge, H. *Die Gastroskopie*, Berlin, Urban & Schwarzenberg, 1937.

16 Lehmann, R. *Les atrophies gastriques dans les anémies idiopathiques et les métanémies*, Paris, E. Le François, 1936.

17 Chevallier, R. *Intérêt de la gastroscopie dans les anémies graves*, Lyon méd **158** 61, 1936.

18 Jones, C. M., Benedict, E. B., and Hampton, A. O. Variations in Gastric Mucosa in Pernicious Anemia, *Am J M Sc* **190** 596, 1935.

successful treatment and that hypertrophic changes also subsided. They suggested, however, that the change from atrophy to normal represents epithelial changes associated with successful treatment of a specific deficiency state rather than the healing of a chronic inflammatory process, while the apparent return to normal from a grossly hypertrophic condition of the gastric mucous membrane represents subsidence of chronic gastritis. We shall reconsider these conceptions in our own conclusions. Evidently these authors were the first directly to observe the complete healing of atrophy of the gastric mucosa as a result of liver therapy.

Since there were so many points of disagreement among the observers using the gastroscope, we decided to compile the data for all our cases of pernicious anemia in which there was no doubt about the diagnosis, considering especially the following questions: 1. What is the nature of the changes in untreated patients? 2. How does the gastric mucosa appear after sufficient therapy? Does the aspect of the mucosa change during therapy? Can it become normal? 3. What is the usual site of the gastric lesions? 4. Is it possible to make some statements concerning such complications as hypertrophic gastritis, the formation of polyps or carcinoma? 5. Do the gastroscopic observations contribute to the theory of the origin of pernicious anemia?

No autopsy material was available. In the 1 case in which death occurred (case 6), necropsy could not be performed. Only such definite changes as are never seen in healthy persons were recorded as abnormal. In almost all instances the so-called 50 degree Wolf-Schindler gastroscope, which has a greater resolving power than the usual 80 degree instrument, was used. All cases in which the diagnosis was uncertain were discarded.

This paper, then, is based on the gastroscopic observation of 23 patients suffering undoubtedly from pernicious anemia.<sup>19</sup> Five of these patients were examined with the gastroscope repeatedly (2 of them twice, 2 of them three times and 1 of them six times), so that a total of thirty-four gastroscopic examinations were carried out on the 23 patients. In order to abbreviate the case reports it is mentioned that all the patients offered a cleancut picture of pernicious anemia, that most of them had some, though often slight, gastric distress and that combined degeneration of the spinal cord of varying degree was often present.

Six of the 23 patients did not receive adequate treatment. Fourteen of these 23 patients were observed only after sufficient or almost suffi-

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19 Ten of these patients were referred by Dr. E. Kandel, head of the hematologic department of the University of Chicago. 1 was referred by Dr. W. L. Palmer, head of the gastrointestinal department at Billings Hospital. 3 were patients of Dr. C. Eiseman of the Oak Forest (Ill.) Hospital. 8 were examined at Michael Reese Hospital and 1 was observed with Dr. Leon Schiff at the Cincinnati General Hospital.

cient treatment Three of the 23 patients were observed first before treatment and then again after sufficient or almost sufficient treatment An additional patient was studied (case 24) in whom pernicious anemia was not found but who had atrophic gastritis which responded to liver therapy This case history seems to be important in connection with the theoretic discussion

The gastrosopic features of the gastric mucosa have been described so thoroughly elsewhere <sup>20</sup> that extensive repetition would be superfluous

#### REPORT OF CASES

##### *A Patients observed gastrosopically who had not had treatment*

CASE 1—A 72 year old man entered the Oak Forest (Ill) Hospital because of weakness, edema of the feet and peculiar sensations in the fingers and toes for about two years Examination revealed typical pernicious anemia The blood count made at the time of the gastrosopic examination showed hemoglobin, 35 per cent, and erythrocytes, 1,950,000 <sup>21</sup>

*Gastrosopic Examination*—The antrum and the body of the stomach presented throughout an atrophic mucosa A few pinkish islands and ridges were observed in the anterior and posterior wall of the body The diagnosis was diffuse atrophy of the entire gastric mucosa

CASE 2—A woman aged 69 was seen at Billings Hospital For two months she had had excessive weakness and fatigue, cramplike pains below the knees, bloating, gaseous belching that was not connected with meals, and rarely nausea and vomiting The clinical features were typical of pernicious anemia The hemoglobin value was 65 per cent, and the erythrocyte count was 1,720,000

*Gastrosopic Examination*—The pylorus contracted energetically, with a mushroom-like protrusion The mucosa of the antrum was definitely gray and thin The musculus sphincter antri was smooth The entire mucosa, increasingly toward the cardia, was thin and gray and contained many thick branching blue and red blood vessels The diagnosis was complete atrophy of the gastric mucosa

*Comment*—The picture in these 2 cases evidently corresponds with that seen by Henning and Gutzeit It is the classic picture of a thin, smooth, gray completely atrophic mucosa, as described by Hayem

CASE 3—A 54 year old woman was seen at Billings Hospital She complained of severe belching, rumbling and gurgling in the abdomen, tingling of the fingers and toes and general malaise The physical examination revealed the typical picture of pernicious anemia plus combined degeneration of the spinal cord The hemoglobin value was 60 per cent and the red blood cell count 2,670,000

*Gastrosopic Examination*—A gastrosopic examination was made, and the diagnosis was complete atrophy of the mucosa of the antrum and patchy atrophic hemorrhagic gastritis of the mucosa of the body of the stomach

20 (a) Schindler, R, Ortmayer, M, and Renshaw, J F Chronic Gastritis, J A M A 108 465 (Feb 6) 1937 (b) Schindler <sup>12</sup>

21 The white blood cell count and the blood smear will not be reported on The latter in cases in which treatment had not been received always was characteristic of pernicious anemia

*Comment*—In this case the antrum was decidedly more atrophic than the body. If one were to observe many similar conditions one would be inclined to agree with Faber's theory that primary inflammation of the pyloric organ is the primary cause of pernicious anemia. The following cases show, however, that this location of mucosal changes is an exception rather than the rule.

**CASE 4**—A 58 year old woman was admitted to Billings Hospital. She complained of loss of weight, loss of appetite, weakness and soreness of the mouth and tongue. Hers was a typical case of pernicious anemia, without changes in the spinal cord. The hemoglobin value was 60 per cent and the red blood cell count 2,460,000.

*Gastrosopic Examination*—A gastrosopic examination was made, and the diagnosis was circumscribed patchy atrophic gastritis of the lower portions of the body of the stomach.

*Comment*—This case proves that there are cases of untreated pernicious anemia in which gross atrophic changes are not seen in the antral mucosa but only patchy atrophy is seen in the mucosa of the body. On the other hand, these patches were not situated close to the cardia but in the distal portions of the body of the stomach.

**CASE 5**—Dr. Leon Schiff permitted us to study this patient at the Cincinnati General Hospital. The clinical findings were those of severe untreated pernicious anemia.

*Gastrosopic Examination*—The pylorus and the antrum were normal. The mucosa of the lower portions of the anterior wall looked slightly granular and thin. Grayish patches were seen in the orange-red mucosa. The upper portion of the stomach was completely atrophic and greenish gray, with two sets of branching blood vessels in the posterior wall.

*Comment*—In this case the most marked atrophic changes were seen close to the cardia, they became less in the lower portions of the body and were absent in the antrum.

**CASE 6**—A 70 year old woman was seen at the Oak Forest (Ill.) Hospital. She had untreated pernicious anemia. Death occurred, but permission for autopsy was not given. The clinical picture was typical of pernicious anemia. The time of the onset of the disease was unknown. The hemoglobin value was 53 per cent and the red blood cell count 2,750,000.

*Gastrosopic Examination*—The first gastrosopic examination was made on Nov. 30, 1936. There were extensive superficial gastritis of the whole stomach (antrum and body), pallor of the mucosa and multiple polyps but no atrophy. The second examination, made on May 13, 1937, showed slight atrophy of the anterior wall of the body, marked superficial gastritis of its upper portion, polyps of the antrum and of the lower portion of the body and a normal mucosa in the antrum.

*Comment*—This case seems to be especially important. The clinical picture was typical of pernicious anemia and the patient later died of this disease. At the first gastrosopic examination, no sign of atrophy was



discovered, but marked superficial inflammation of all portions of the gastric mucosa was noted. Later, this superficial inflammation was seen only in the upper portions of the body, while some portions of the mucosa of the body had become definitely atrophic. The mucosa of the antrum, however, had become normal, although no treatment had been given. This observation proves that there are cases of pernicious anemia in which superficial gastritis is present without any visible atrophy and that atrophy following this superficial inflammation can occur at a later stage. One may argue that the superficial epithelial cells might already have been changed by some regressive process, which then facilitated infection and subsequent severe inflammation. This, however, is hypothetical, and it would be impossible to prove or to contradict such a conception. It is certain that atrophy of the mucosa itself—thinning and graying—was not present, although pernicious anemia was marked and advanced. Furthermore, definite atrophy developed later, while superficial gastritis was found only in the upper portions of the mucosa of the body. Finally, the superficial gastritis of the antrum subsided without changing into atrophy. We are inclined to consider this case as proof that the atrophy, both the patchy and the diffuse form, seen in patients with pernicious anemia is inflammatory rather than purely regressive. It is interesting that the superficial gastritis led to atrophic gastritis only in the body, whereas the antrum became normal. The frequency of benign tumors in cases of pernicious anemia is well known. It is remarkable that in this case benign polyps were found in an inflamed but not atrophic mucous membrane.

*B Patients observed gastroscopically after having had liver therapy*

CASE 7—A 54 year old man was admitted to Michael Reese Hospital. For one year he had complained of headache, weakness, pains in the legs and loss of weight. He was pale, and the tongue was atrophic. The complete picture of pernicious anemia was found, the hemoglobin value being 60 per cent and the red blood cell count 1,780,000. After systematic treatment with liver the hemoglobin value was 80 per cent and the red blood cell count 4,440,000. The tongue had become normal. The patient's general condition was good.

*Gastroscopic Examination*—The gastroscopic examination revealed extensive patchy atrophic gastritis of the antrum and lower parts of the body of the stomach.

*Comment*—In this case, in which marked atrophic changes similar to those in untreated patients were present, it is impossible to decide whether the condition of the gastric mucosa had improved as a result of treatment. That the treatment had been rather satisfactory was proved not only by the hematologic findings but also by the return of the tongue to normal. Evidently in this case there was no parallel between the condition of the tongue and that of the gastric mucosa.<sup>22</sup>

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22 Chevallier, P., and Moutier, F. *Langue et estomac*, Presse méd. 43 1801, 1935.

CASE 8—A 58 year old patient was admitted to Michael Reese Hospital, complaining of weakness, numbness and tingling in the extremities, dyspnea, edema, nausea and loss of weight for one year. Before treatment the tongue was smooth, no free hydrochloric acid was found in the stomach contents, the hemoglobin value was 27 per cent and the red blood cell count was 1,000,000.

*Gastrosopic Examination*—At the time of the gastrosopic examination the hemoglobin value was 85 per cent and the red blood cell count 4,790,000. The gastrosopic diagnosis was extensive diffuse atrophic gastritis of the whole stomach.

*Comment*—In this case the treatment had been sufficient, yet all portions of the stomach showed marked atrophic gastritis.

CASE 9—A 56 year old woman was admitted to Michael Reese Hospital. She had had burning epigastric sensations for eighteen months. Dyspnea developed, and the gastric pain became severe. She became weak and tired easily and had nausea and vomiting. Physical examination showed the typical picture of pernicious anemia. After liver treatment the hemoglobin value rose from 35 to 75 per cent and the red blood cell count from 1,400,000 to 4,120,000.

*Gastrosopic Examination*—At the time of the gastrosopic examination she complained of only slight gastric pain. The diagnosis was diffuse, almost complete atrophic gastritis of the whole stomach.

*Comment*—It may be that in this case the treatment had not been sufficiently energetic. It is noteworthy that the subjective condition and the blood picture made such great strides forward while the gastric mucosa remained so completely atrophic that improvement as a result of therapy could scarcely be assumed.

CASE 10—A 32 year old man had been treated for pernicious anemia for seven years (1930 to 1937). At the time of gastrosopic examination at Billings Hospital he felt fine. With liver therapy the hemoglobin value had increased from 30 to 90 per cent and the red blood cell count from 1,370,000 to 5,700,000.

*Gastrosopic Examination*—The gastrosopic diagnosis was extensive, almost complete atrophic gastritis of the antrum and the body.

*Comment*—In this case the therapy had been sufficient. The blood picture was normal, and the patient felt fine, nevertheless, the gastric mucosa showed almost complete diffuse atrophic gastritis.

In the following 5 cases the mucosal changes were less marked.

CASE 11—A 47 year old woman was seen at Michael Reese Hospital. She had suffered from anorexia, weakness and dizziness for six years. Typical pernicious anemia was detected, and liver therapy was given. At the time of gastrosopic examination, the condition had much improved. The hemoglobin value was 80 per cent and the red blood cell count 4,300,000.

*Gastrosopic Examination*—In the greater curvature of the antrum a small, reddened prominence (polyp) was seen. In the lesser curvature of the body some parallel folds were present. The valleys between them presented a thinned, grayish mucosa. All other portions of the body had a normal appearance. The diagnosis was slight patchy atrophic gastritis of the lesser curvature of the body. There was a small polyp in the antrum.

*Comment*—This result of sufficient liver therapy corresponds well with the results obtained by P Chevallier and Moutier and by Lehmann

CASE 12—A 35 year old man was seen at Michael Reese Hospital He complained of exhaustion, loss of weight, anorexia, abdominal pressure and soreness of the tongue for four months The physical examination revealed the complete picture of pernicious anemia The tongue was atrophic, anacidity was demonstrated by the histamine test The hemoglobin value was 45 per cent and the red blood cell count 1,150,000 Injections of liver extract were given and the condition improved considerably

*Gastroscopic Examination*—At the time of the gastroscopic examination the hemoglobin value was 72 per cent and the red blood cell count 4,300,000 The gastroscopic diagnosis was patchy atrophic gastritis of the body only The antrum was normal

*Comment*—In this case also the extensive atrophic patches were found only in the body of the stomach

CASE 13—A 72 year old man was admitted to Billings Hospital He complained of loss of weight, swelling of the ankles, numbness and tingling in the hands and feet, difficulty in walking, and itching The diagnosis was pernicious anemia with combined degeneration of the spinal cord He had had some liver treatment for one year before entry, so that the original figures for the hemoglobin and red blood cells were not available However, the blood count was about normal hemoglobin, 99 per cent, and red blood cells, 4,560,000

*Gastroscopic Examination*—The gastroscopic diagnosis was slight patchy atrophic gastritis of only the distal portions of the stomach There was one small mucosal hemorrhage

*Comment*—In this case the typical changes were almost completely absent However, remainders were observed in the antrum and in the lower portions of the stomach

CASE 14—A 61 year old patient was admitted to Billings Hospital He had been treated for three years for pernicious anemia and combined degeneration of the spinal cord In the beginning the hemoglobin value was 50 per cent and the red blood cell count 2,480,000 After injections of liver extract the blood had become normal Before the gastroscopic examination the hemoglobin value was 103 per cent and the red blood cell count 4,900,000

*Gastroscopic Examination*—The gastroscopic diagnosis was extensive, patchy atrophic gastritis of only the anterior wall of the body

*Comment*—In this case the blood picture was completely normal Nevertheless, extensive atrophic changes were observed, but only in the anterior wall of the body, the antrum was normal

CASE 15—A 49 year old man was seen at Billings Hospital One year previously, pernicious anemia had been discovered His complaints were of weakness and sore throat At that time the red blood cell count was as low as 2,000,000 A histamine test showed anacidity After injections of liver extract for five years the blood picture became normal and remained so

*Gastroscopic Examination*—At the time of the gastroscopic examination the hemoglobin value was 98 per cent and the red blood cell count 4,650,000. Gastroscopic examination revealed that the mucous membrane, especially in the upper portions, was thinner than normal, with gray spots and small blood vessels. These changes were not striking.

*Comment*—This patient had been well treated for pernicious anemia and showed a normal blood picture. However, there was slight but definite patchy atrophic gastritis in the upper portion of the stomach.

**CASE 16**—A 51 year old patient was admitted to Michael Reese Hospital. He had been examined seven years previously, and at that time the typical picture of pernicious anemia was found. The hemoglobin value was 60 per cent and the red blood cell count 2,700,000. He then received liver therapy regularly. Signs of degeneration of the spinal cord were found later. The administration of liver had lately been rather irregular. The blood picture, however, was satisfactory.

*Gastroscopic Examination*—At the time of the gastroscopic examination the hemoglobin value was 90 per cent and the red blood cell count 4,430,000. The gastroscopic diagnosis was as follows: slight patchy atrophic gastritis of the anterior wall and marked superficial gastritis of the fornix.

*Comment*—It will be noted that in all the 6 patients who received sufficient or almost sufficient treatment and who showed only patchy atrophic areas at gastroscopic examination, these patches were located in the body, the antrum being free. The only exception was case 13, in which the antrum also was involved. It should be borne in mind, however, that exclusive involvement of the antrum may occur in cases of untreated pernicious anemia (cases 4 and 5). In the last described case (case 16) superficial gastritis of the fornix was seen. In order to avoid misinterpretation one should be aware that superficial gastritis can be found alone and preceding atrophy in cases of untreated pernicious anemia (case 6). It is not likely that this finding was caused by the treatment in this case.

**CASE 17**—A 74 year old man was examined gastroscopically six times at Michael Reese Hospital. He was first seen two years before the first gastroscopic study. At that time he complained of weakness, loss of weight, epigastric distress and nausea. The physical examination revealed pallor, an atrophic tongue and absence of free hydrochloric acid with the histamine test. The blood picture was that of pernicious anemia, the hemoglobin value being 52 per cent and the red blood cell count 2,690,000. After liver treatment the blood findings were as follows:

Gastroscopic Study	Hemoglobin, %	Red Blood Cell Count, Thousands
1	75	4,140
2	82	4,140
3	77	4,350
4	69	4,110
5	60	4,280
6	70	4,180

*Gastrosopic Examination*—The six gastrosopic studies were carried out within one year (November 1936 to October 1937), and the following reports were made

Nov 12, 1936 The entire stomach was seen The mucosa of the antrum was normal but contained three prominent hemispheric "stalagmite" polyps The mucosa of the body was covered with small amounts of adherent mucus but was not atrophic In the middle of the body, in its posterior wall toward the greater curvature, another polyp was seen It had a broad base and was dark red and somewhat ulcerated A fifth polyp with a broad base was seen beneath the cardia At this time definite superficial gastritis without atrophy was seen

Jan 15, 1937 At this examination additional polyps were observed The pyloric action was normal In the antrum six polyps were seen A seventh was in the posterior wall of the midportion of the stomach It was dark red and contained many yellow ulcerations The eighth was high up on the posterior wall, about 4 cm below the cardia It had a broad base and was reddened and partly ulcerated All other portions of the mucous membrane were normal At this examination the superficial gastritis had disappeared No atrophy was observed The mucosa was not pale The number of polyps had increased The appearance of two of them was highly suggestive of beginning malignant growth

Feb 16, 1937 The mucous membrane was normal Most of the polyps were unchanged However, the seventh one apparently had grown Its surface was irregular and nodular and was covered with whitish mucus The eighth (highest) polyp had not grown but had such an irregular shape that without the other appearance of polyposis we would have made a diagnosis of beginning carcinoma

April 16, 1937 At this examination only the upper polyps were well visualized The mucous membrane looked normal

May 20, 1937 The color of the mucus membrane appeared normal, the mucosal folds were normal The appearance of the polyps had not changed

Oct 1, 1937 There was marked superficial antral gastritis

*Comment*—This patient may not have been treated sufficiently Nevertheless, at none of the six gastrosopic examinations was any sign of atrophy discovered Twice, however, at the first and at the sixth examination, definite superficial gastritis was seen Without the knowledge of the condition in untreated pernicious anemia (case 6) we would have considered that these periods of superficial gastritis were due in some way to the treatment That case has taught us that the same picture may be found without any treatment Eight polyps were present Malignant degeneration was not observed, although two of the tumors were highly suggestive of beginning malignant growth In almost every case of benign tumor of the gastric mucosa, accompanying atrophic gastritis is found gastrosopically Therefore, it must be assumed that the absence of atrophic changes in this case was due to the liver therapy

In the 3 following cases no pathologic changes were seen after successful treatment

CASE 18—A 36 year old woman was admitted to Billings Hospital She was seen first in 1933, when she complained of dizzy spells, indigestion and extreme nervousness The blood picture showed the characteristics of pernicious anemia The hemoglobin value was 57 per cent and the red blood cell count 1,990,000

No free hydrochloric acid was found. She recovered after receiving liver therapy. In 1935 the hemoglobin value was 106 per cent and the red blood cell count 5,480,000.

*Gastroscopic Examination*—Gastroscopic examination showed that the stomach was normal.

*Comment*—In this case there was slight polycythemia after treatment for severe pernicious anemia. The gastric mucosa was normal.

CASE 19—A man aged 38 had entered Billings Hospital in 1933 and had been under treatment in the hematologic department since then. His chief complaint was of weakness. He had slight evidence of degeneration of the spinal cord, there was no free hydrochloric acid in the gastric contents and the blood picture was typical of pernicious anemia, the hemoglobin value being 60 per cent and the red blood cell count 2,540,000.

*Gastroscopic Examination*—Gastroscopic examination revealed that the stomach was normal.

CASE 20—A 58 year old woman was admitted to Billings Hospital in 1932 and was under observation until 1936. Her chief complaints in the beginning were of weakness, numbness of the extremities and severe headache. A diagnosis of pernicious anemia with mild combined degeneration of the spinal cord was made. No free hydrochloric acid was found. The hemoglobin value was 51 per cent and the red blood cell count 2,080,000. After liver therapy and at the time of the gastroscopic examination the blood count showed hemoglobin, 95 per cent, and red blood cells, 4,220,000.

*Gastroscopic Examination*—Gastroscopic examination revealed that the stomach was normal.

*Comment*—While the patients in cases 18 and 19 perhaps were somewhat "overtreated," the blood count in case 20 was normal, and normal gastric mucosa was found gastroscopically. One should compare this case with cases 7, 8 and 10, in which the blood picture had become entirely normal but the gastric mucosa was still almost completely atrophic. Only the findings in cases 18, 19 and 20 agree with those presented by Jones, Benedict and Hampton<sup>18</sup>.

#### *C Patients observed gastroscopically before and after liver therapy*

CASE 21—A man aged 70 was admitted to Oak Forest (Ill.) Hospital. He was first seen immediately before the gastroscopic examination. He was completely deaf. He was anemic and had edema of the legs and signs of combined degeneration of the spinal cord. No free hydrochloric acid was found in the gastric contents. The hemoglobin value was 37 per cent and the red blood cell count 1,280,000. The blood smear showed changes typical of pernicious anemia.

*Gastroscopic Examination*—On Nov. 28, 1936, examination revealed extensive atrophic gastritis of the whole stomach.

The patient was then given liver therapy. Either the dosage was not adequate, or the patient did not react to liver. Half a year later the hemoglobin value was 73 per cent and the red blood cell count 3,710,000. The smear still showed achromia and anisocytosis. However, the gastroscopic picture had changed entirely. On May 13, 1937, examination showed marked regression of the atrophic gastritis. There was slight atrophic hemorrhagic gastritis of the highest portion of the lesser curvature.

*Comment*—In this case regeneration of a previously atrophic mucous membrane could be followed in its stages by repeated gastroscopic examination. The end result of this regeneration had been observed in cases 18, 19 and 20. The blood picture returned almost to normal. The mucous membrane of the distal portions of the stomach appeared to be normal, and only the upper portion of the lesser curvature showed atrophic hemorrhagic inflammation. In cases 18 to 21 the mucous membrane was definitely normal, there was none of the overlapping, thickening or inflammation described by Gutzeit and Teitge.<sup>15</sup> A real regeneration had taken place.

Still more impressive was the following case.

CASE 22—A 53 year old woman was admitted to Michael Reese Hospital. She was first seen in 1934, when she said she had had progressive weakness for two years, uncomfortable fulness after meals, nausea and vomiting. Pernicious anemia was diagnosed because of the characteristic blood picture, i. e., a hemoglobin value of 45 per cent and a red blood cell count of 1,410,000. After liver therapy her condition improved considerably (hemoglobin value, 80 per cent, red blood cell count, 4,400,000). Between June and October 1936 she voluntarily stopped treatment, and consequently the hemoglobin value dropped to 45 per cent and the red blood cell count to 2,050,000.

*Gastroscopic Examination*—Examination on Nov. 5, 1936, showed pallor of the mucosa, atrophic gastritis of the antrum and of the upper portions of the body, and some small mucosal hemorrhages.

The distribution of the atrophic changes at this observation is noteworthy. The antrum and the upper portions of the body were atrophic, and the lower portion of the body, usually the seat of the most outspoken change, was normal.

The next gastroscopic examination was carried out about one month later, after liver therapy. The hemoglobin value then was 72 per cent and the red blood cell count 3,560,000. An almost normal blood picture had been attained.

A second gastroscopic examination, on Dec. 7, 1936, showed disappearance of pallor, disappearance of atrophic gastritis of the antrum, atrophic gastritis of the upper portions of the body and one mucosal hemorrhage in the posterior wall.

About two months later the blood picture was normal, the hemoglobin value being 90 per cent and the red blood cell count 4,940,000. In this short time the gastroscopic picture had changed entirely. A third gastroscopic examination, on Feb. 11, 1937, showed that the stomach was normal.

*Comment*—In this case the changes in the gastric mucosa as a result of liver therapy were observed at three gastroscopic examinations. At first the antrum was atrophic, and the upper portions of the body presented marked patchy atrophic gastritis. After one month of treatment the antral mucosa had become normal, whereas the mucosa of the body still presented definite atrophic gastritis. After three months of treatment, complete regeneration had taken place.

CASE 23—A 61 year old patient was admitted to Billings Hospital. The chief complaints were of difficulty in walking and numbness of the hands and legs. The findings were typical of pernicious anemia with combined degeneration of the

spinal cord At the time of the first gastroscopic examination the hemoglobin value was 75 per cent and the red blood cell count 2,720,000 No free hydrochloric acid was found

*Gastrosopic Examination*—At the first gastroscopic examination, on April 3, 1935, two patches of atrophic gastritis in the lower portion of the body and in the fornix were observed

Eighteen days later, after liver therapy, the hemoglobin value was 82 per cent and the red blood cell count 3,300,000

A second gastroscopic study was made, on May 14, 1935 The body of the stomach presented exactly the same picture as at the previous examination, i e, there were two atrophic areas In the antrum were some stiff folds

After continued liver therapy the hemoglobin value rose, within an additional two months, to 99 per cent and the red blood cell count to 4,620,000

A third gastroscopic examination on July 23, 1935, revealed complete atrophy of the upper portions of the body and marked hypertrophic gastritis of the greater curvature of the antrum

*Comment*—The findings in this case are different from those in all the others Before the beginning of any therapy only two atrophic patches in the body of the stomach were seen After the blood picture had become normal, with adequate therapy, it was found that the atrophic areas had increased in size considerably, at the same time hypertrophic changes had developed in the antrum The occurrence of hypertrophic gastritis in this case may perhaps be explained by some kind of overcompensation by the mucosa But there is no explanation as to why such compensation was not found in any of the other 21 cases Another important point is the progression of the atrophic changes, in spite of liver therapy This will be discussed later It is easy to understand that anatomic degenerative changes caused by a deficiency status may become stationary and even irreversible after the disappearance of the deficiency status It is impossible for us to understand why such degenerative changes should continue after the elimination of the deficiency status, if we are not willing to assume that they are effected, at least partly, by chronic progressive inflammation This is proved especially by case 10

*D A patient with chronic atrophic gastritis which responded to liver therapy*

This patient does not properly belong to our group of patients with pernicious anemia The case will be discussed briefly because it appears to be essential with reference to the theoretic questions arising from the observations of other authors and from our own observations P Chevallier observed patients suffering from unexplainable fatigue and abdominal distress in whom atrophic gastritis was found gastroscopically and for whom liver therapy gave the most gratifying results He perceived here, correctly, a definite relation to the classic picture of hyperchromic anemia He therefore chose the term anemia without anemia,



or metanemia, to designate this clinical picture. In our opinion this nomenclature is not accurate. It is misleading to call a disease anemia, even with the prefix meta, if no anemia is present. Furthermore, the most important feature of real pernicious anemia is missing in these cases, namely, the malignant character, with the fatal course. We desire to be careful in evaluating these cases and deem it better to call them cases of chronic atrophic gastritis caused by a deficiency state. We feel sure that this category later must be split up. There are probably many cases in which atrophic gastritis is caused by a deficiency state without any relation to that found in pernicious anemia. Here these cases will not be considered. If, however, a patient with atrophic gastritis responds to liver treatment, then a certain if even remote relation to pernicious anemia scarcely can be denied. Therefore, we shall discuss the following case.

CASE 24—A 49 year old woman was seen at Billings Hospital. Since 1932 she had been treated for "chronic functional colitis." Her chief complaints were of epigastric pains, chronic constipation, severe generalized headache, dizziness and vomiting. For several years she also had had numbness of the feet and hands and some vague soreness of the mouth and tongue. Hunger pains were observed, sodium bicarbonate giving some relief. She complained of belching and bloating. For five years she had been taking cathartics. After defecation she felt relieved. Her appetite was fairly good. She had considerable chronic fatigue and nervousness.

The physical examination was essentially unimportant. A histamine test showed an acidity. The blood picture was normal, the hemoglobin value being 80 per cent and the red blood cell count 4,550,000. The blood smear did not show any abnormality.

The patient was followed for three years, and no definite improvement occurred. A careful examination of the nervous system did not reveal definite evidence of combined degeneration of the spinal cord. Repeated histamine tests confirmed the absence of free hydrochloric acid. No pathologic condition was revealed roentgenographically.

*Gastroscopic Examination*—The first gastroscopic study was made on July 12, 1935. It revealed marked atrophic gastritis of the body of the stomach. At that time the hemoglobin value was 82 per cent and the red blood cell count 4,680,000. A second gastroscopic study was carried out, on March 24, 1936. At that time the hemoglobin value was 85 per cent and the red blood cell count 4,900,000. There was marked atrophic hemorrhagic gastritis of the entire body of the stomach. In other words, the mucosa of the stomach offered essentially the same aspect that it had nine months before. After this observation, injections of liver extract were given regularly. After about three months of this treatment the patient felt much better. Most of her distress had disappeared. The blood picture was unchanged, but a third gastroscopic examination, carried out on June 15, 1936, showed an entirely different condition. The stomach was normal. Regeneration of the previously atrophic mucous membrane had followed the institution of liver therapy.

This regeneration of a previously atrophic mucosa following liver therapy naturally was considered to be an amazing event. Liver treatment was continued

for several months. However, when we examined the patient the fourth time, on Oct 28, 1936, we did not know that she had discontinued the therapy for more than four weeks and were surprised to find a marked relapse. The blood count at that time showed a hemoglobin value of 71 per cent and a red blood cell count of 4,900,000. Gastroscopic examination revealed patchy atrophic hemorrhagic gastritis of the body, which was less marked than at the first gastroscopic examination.

*Comment*—In this case the cessation of liver therapy for several weeks had sufficed to cause a marked relapse. It must be emphasized that we have observed several patients with diffuse atrophic gastritis without hematologic changes on whom liver therapy had no effect at all. It is impossible to decide whether simple inflammation, perhaps a sequel to superficial gastritis, had been present or whether a deficiency state had also been present, the deficiency being different from that found in pernicious anemia (as for instance, lack of iron or vitamin A or B).

#### COMMENT

The peculiarities of the cases described have already been briefly discussed. The findings may be summarized as follows:

1 *Kind and Site of the Gastric Lesions*—In 9 cases of untreated pernicious anemia (cases 1 to 6 and 21 to 23) no case was found in which the gastric mucosa was normal. In 8 of these cases the typical signs of atrophic gastritis were observed. The well known picture of atrophy of the entire mucosa (of the body as well as of the antrum) was observed in only 3 cases (cases 1, 2 and 21). In 2 cases (cases 3 and 22) patchy gastritis of both the antrum and the body was observed, in case 3 the antrum most decidedly was more affected than the body. In 3 cases (cases 4, 5 and 23) the antrum was normal, but marked patchy atrophic gastritis was found in the body.

In 1 case (case 6) the findings were peculiar and of great interest theoretically. At the first examination, extensive superficial gastritis of the entire stomach was seen. At the second examination some patches of atrophy had developed in the body, superficial gastritis was still present in the fornix and the antrum had become entirely normal, nevertheless, the patient died a short time later of untreated pernicious anemia.

Seventeen patients were observed gastroscopically after having had adequate or almost adequate treatment (cases 7 to 23). Three of them had been examined with the gastroscope before treatment. In 4 of these 17 cases (cases 7 to 10, in 3 of which adequate treatment had been given) marked atrophic changes were found in the gastric mucosa. It is evident that in these cases liver treatment influenced the blood-forming organs but not the gastric mucosa. It is a curious fact that in 1 of these cases not only the blood count but the tongue had also

become normal, whereas the atrophic gastric mucosa had not responded to liver therapy

The 6 following cases (cases 11 to 16) have in common the fact that after sufficient treatment the antral mucosa seemed to be normal while some portions of the mucosa of the body presented more or less extensive patchy atrophic areas. In the last of these cases there were superficial gastritis of the fornix and slight patchy gastritis of the body, so that the picture agreed exactly with that in case 6, in which liver therapy was not given. It is not possible to state definitely that in any of these cases the treatment which had altered the blood picture and had kept the patients alive had had any influence on the gastric mucosa.

In 4 patients (cases 17 to 20) the gastric mucosa was entirely normal. This normality must be attributed to the treatment, because in untreated patients a normal mucosa is never observed. Three of these patients had been treated energetically. One of them (case 17) in whom the treatment had been less energetic was examined six times. A normal gastric mucosa was found four times, and marked superficial gastritis was seen on two occasions. (The question of the benign polyps found at each of these examinations will be omitted in this connection.)

If cases 6, 16 and 17 are compared, it must necessarily be concluded that superficial gastritis without atrophy is the primary visible lesion and that atrophic changes develop after this primary superficial inflammation.

In cases 21 to 23 observations were made before and after liver therapy. In case 21 the extensive, complete atrophy of the stomach disappeared after liver therapy except for a few atrophic patches in its highest portion. This observation seems to point to the fact that the normal mucosa seen in cases 17 to 20 was due to the influence of liver therapy, i. e., in some cases of pernicious anemia a previously atrophic mucosa may regenerate to a normal macroscopic aspect with liver treatment. These observations correspond with those made by Jones, Benedict and Hampton<sup>18</sup>. It should be emphasized again that this regeneration takes place in only a fraction of all the cases studied.

One patient (case 22) was observed three times and always showed the same phenomenon, though to a lesser extent. The antral mucosa, which at first was markedly atrophic, became normal, whereas the body mucosa remained atrophic. We have gained the impression that the regenerative process is more likely to develop in the antrum than in the body. It should be remembered that in one third of the untreated patients the antrum was not affected at all, the pathologic changes being present only in the body.

Finally, 1 patient (case 23) not only failed to show any improvement of the gastric atrophy under entirely satisfactory treatment but,

on the contrary, when the blood picture had become normal, the atrophy had increased considerably in size. This observation, in our opinion, speaks most definitely against the mere regressive degenerative character of the gastric atrophy in pernicious anemia. In the same case, hypertrophic changes of the antrum developed. It may be that they constitute a kind of compensatory reaction, but it seems to us better not to speculate about their nature, since their exact character was not proved by repeated observations or by histologic study.

In 2 cases (cases 6 and 17) multiple polyps of the gastric mucosa were observed, in 1 case a solitary polyp was seen (case 11).

*2 Theoretic Considerations*—The following observations must be considered

1 No patient with untreated pernicious anemia showed a normal stomach at gastrosopic observation. However, it seems to be certain that the primary visible lesion is superficial gastritis.

2 The more or less extensive atrophic changes are found either throughout the stomach or in the body alone, the antrum sometimes may be free from changes.

3 Sufficient liver therapy may lead to one of three end results with respect to the atrophy: (1) a reversal of the atrophic changes, the gastric mucosa becoming normal, (2) no change, or (3) advancement of the atrophic changes during the treatment.

We know that in pernicious anemia a hormone is missing which may be substituted for by liver therapy. The main source is the gastric mucosa or, more specifically, the mucosa of the antrum and the duodenum ("pyloric organ," Brunner glands), although it may be admitted that other portions of the stomach or even of the intestine or other organs may produce minor quantities of this hormone (see the fundamental papers by Whipple and Robschey-Robbins,<sup>13</sup> Minot and Murphy<sup>23</sup> and Castle<sup>9</sup>). Since changes of the gastrointestinal mucosa are found in all cases of pernicious anemia, a connection between these two facts appears probable. Faber<sup>10</sup> drew the apparently inescapable conclusion that chronic gastritis is the primary disease affecting the function of the "pyloric organ," thereby producing the clinical picture of pernicious anemia. Although this theory seems to be sound, it nevertheless cannot be reconciled with our observations. It is true that the changes observed are inflammatory changes. Nevertheless they cannot be the cause of the destruction of Castle's intrinsic factor because (1) superficial as well as atrophic changes are most pronounced in the upper

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<sup>23</sup> Minot, G. R., and Murphy, W. P. A Diet Rich in Liver in the Treatment of Pernicious Anemia. Study of One Hundred and Five Cases. *J. A. M. A.* 89: 759 (Sept. 3) 1927.

portions of the stomach and often are entirely absent from the antrum and (2) in some cases (the cases reported on by Jones, Benedict and Hampton<sup>18</sup> and our own cases) complete reversion of the atrophic process can take place. It is almost unbelievable that an inflammatory process of unknown origin should destroy the gastric mucosa to such an extent as to prevent the formation of a hormone and that this same inflammatory process should be healed by the administration of exactly the same hormone.

The only possible conclusion is that in pernicious anemia one is dealing with two different diseases of the gastric mucosa: a primary disease, probably invisible and concerning those portions of the gastric mucosa which form the intrinsic "antianemic" factor, and a secondary disease, developing because of the lack of the intrinsic factor which produces the typical syndrome, namely, pathologic changes in the tongue, the pharynx, the blood and the nervous system (Guillaume<sup>24</sup>). These secondary changes respond in a different way to the administration of the missing hormone. The blood may become normal, whereas the inflammation may remain stationary or may even advance, the blood picture and the tongue may become normal, the gastric atrophy remaining unchanged, or the blood picture may become normal, and the gastric mucosa, at the same time, may become normal, too.

How can a deficiency state produce inflammation of a mucous membrane? The best paradigm of such a condition is xerophthalmia. It is well known that xerophthalmia is caused by lack of vitamin A. It can be produced artificially and studied microscopically at an early stage, a status which is impossible in the mucosal manifestations of pernicious anemia. The following progression has been established: primary degeneration of the epithelium cells of the cornea<sup>25</sup> leading to secondary inflammation. We believe that the gastric mucosa follows a similar evolution in pernicious anemia. The first event is the dysfunction of the cells which produce the intrinsic factor. We do not know the cause of this dysfunction. The second and consequent event is a degenerative process of the surface epithelium of the gastric mucosa. This stage can never be observed, since it occurs so early. It is therefore not known whether it would be possible to see the degeneration macroscopically, for instance, because of a loss of transparency. A degenerated surface epithelium may immediately give way to secondary inflammation due to chemical irritation or to bacteriologic infection. Superficial gastritis develops, and this may sometimes be observed gastroscopically. The

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24 Guillaume, A. C. Etude physiopathologique sur le rôle hématopoïétique de l'estomac, *Arch. d. mal. de l'app. digestif* 26:241, 1936.

25 Tassman, I. S. Dietary Deficiency and Ocular Disease, *Arch. Ophth.* 8:580 (Oct.) 1932.

tendency to heal, if the surface epithelial cells have regained their protective power as a result of adequate treatment, seems to be much greater in the antrum than in the body. If no therapy is given, the superficial gastritis usually turns into atrophic gastritis. This development is common in cases of nonspecific chronic superficial gastritis without pernicious anemia and has been described<sup>26</sup>. After the administration of adequate treatment at this point, two types of development have been observed. Either the gastric cells are irreparably damaged by the inflammation, and the atrophy persists or even proceeds, or there are enough normal cells left to serve as a nucleus for complete regeneration.

We have already mentioned that the fact that the atrophy may proceed, in spite of sufficient elimination of the deficiency state, seems to us to prove its inflammatory rather than its purely degenerative nature. If this were merely a regressive process due to a deficiency state, one could expect that it would become stationary after the elimination of the deficiency state. It is impossible for us to understand how such a regressive process could become worse after the elimination of the deficiency state. On the other hand, if it is assumed that the atrophic process is not a degenerative but an inflammatory one, the difficulty of explaining the phenomenon is eliminated. An inflammation depending on factors other than the deficiency state alone (infection or irritation) could proceed even after sufficient amounts of the missing hormone had been given. We believe that the observations in case 23 are definite proof that the atrophic changes found in patients with pernicious anemia are of inflammatory rather than of purely degenerative origin.

The question arises: What happens to the gastric function during regeneration of the mucous membrane? Three possibilities must be considered. 1. The anacidity is a consequence of the existing gastritis; anacidity is often found in superficial as well as in atrophic gastritis. One would conclude that the function of the acid-secreting cells should return after the regeneration of the gastric mucosa. Faber and also Alsted<sup>27</sup> have mentioned such cases, but unfortunately gastroscopic examinations were not made. 2. The acid-secreting cells are damaged by the same process which caused the cessation of the secretion of the intrinsic factor. In that case, reparation of function does not seem to be likely. 3. Or, finally, the anacidity is a constitutional hereditary anomaly.

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26 Schindler, R., and Ortmyer, M. Classification of Chronic Gastritis with Special Reference to the Gastroscopic Method. Study Based on One Thousand Two Hundred Cases, *Arch. Int. Med.* **57**: 959 (May) 1936. Schindler<sup>12</sup>, Schindler, Ortmyer and Renshaw<sup>20a</sup>.

27 Alsted, G. On Free Hydrochloric Acid in the Stomach in Pernicious Anemia, *Acta med. Scandinav.* **82**: 288, 1934.

(Hurst<sup>11</sup>), a factor essential for the origin of pernicious anemia. It seems that in families of patients suffering from pernicious anemia, not infrequently other members are found who also present histamine-fast anacidity. Since so few cases have been reported in which the anacidity disappeared after the institution of liver therapy, whereas complete regeneration of the gastric mucous membrane certainly is not a rare event, we are more inclined to accept one of the two latter theories than to attribute the anacidity to the gastritis.

It has been mentioned that the deficiency state leads to a definite syndrome, consisting of inflammation and atrophy of the tongue, the pharynx, the stomach and the intestine and changes in the blood picture and in the nervous system, especially combined degeneration of the spinal cord. However, it is likely that there are cases in which the same deficiency does not produce all the links of this chain. The most dangerous one, the dysfunction of the hemopoietic apparatus, may be missing. There are perhaps cases in which severe atrophy of the gastric mucosa is found linked with combined degeneration of the spinal cord. One should remember the fact that atrophic gastritis is found in sprue and that this disease responds to liver treatment. In addition, we were able to present a case (case 24) in which severe atrophic gastritis responded to liver therapy, with complete regeneration, in this case only scarcely perceptible signs of degeneration of the spinal cord and only once slight anisocytosis were noted. It remains to be seen in how many cases atrophic gastritis (epigastric distress, belching, fulness, general weakness and nervousness—common symptoms of atrophic gastritis) can be healed by the administration of liver.

It is well known that mucosal tumors, polyps and carcinoma are frequent in pernicious anemia, so that it is not surprising that we found typical apparently noninflammatory adenoma in 3 of our cases.

#### SUMMARY

Gastroscopic observations are presented for 23 patients with pernicious anemia. Nine of these patients were seen before any treatment had been given, 14 were observed only after adequate treatment and 3 were examined before and after treatment.

All untreated patients presented superficial gastritis, superficial plus atrophic gastritis or patchy or diffuse atrophy.

After treatment in 4 cases no marked improvement of the condition of the gastric mucosa was found, in 1 case there was definite progression of the atrophy, in 7 cases the mucosa of the antrum was found to be normal, in 1 case there was almost complete regeneration and in 4 cases all portions of the gastric mucosa became normal.

These facts can be explained only by the assumption that in pernicious anemia two separate diseases of the stomach are present. Primarily there is dysfunction of the cells which produce the "antianemic" factor. Secondly there follows degeneration of the surface epithelium, with superimposed genuine inflammation which may or may not heal when the deficiency state is eliminated.

The secondary inflammation usually is combined with a similar disorder of the tongue and of the intestine, with dysfunction of the hemopoietic apparatus and combined degeneration of the spinal cord. However, the absence of the "antianemic" factor may sometimes lead to severe but reversible atrophic gastritis, without disease of the blood. If this observation is confirmed, the expression antianemic must be replaced by another term.

Probably in many cases atrophic gastritis is due to some kind of deficiency state and in some of them to the lack of the "antianemic" factor. This disease should be diagnosed by the use of the gastroscope, and in each case that is discovered liver therapy should be given tentatively. Gastrosopic check of the result of therapy is necessary.

The frequent incidence of mucosal polyps of the stomach in pernicious anemia is corroborated by our observations.



# Progress in Internal Medicine

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## DISEASES OF METABOLISM AND NUTRITION

### REVIEW OF CERTAIN RECENT CONTRIBUTIONS

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### I DISEASES OF METABOLISM

By DR WILDER AND DR RUTLEDGE

#### ENDOCRINE RELATIONS IN DIABETES MELLITUS

The primary contribution of the past year to the physiology of diabetes mellitus was the demonstration by Frank George Young,<sup>1</sup> of University College, London, that *lasting* diabetes can be produced in dogs by injection of anterior pituitary extract. The preliminary report appeared in August 1937, publication of satisfactory details was made in March 1938. Hyperglycemia and glycosuria had been obtained before with similar extracts by Evans and his associates<sup>2</sup> (1932) and by others, including Houssay and his colleagues,<sup>3</sup> but the glycosuria in their experiments was impermanent and persisted only as long as daily injections were maintained, never much longer. Such transitory glycosuria, even with hyperglycemia, does not constitute diabetes. It can be provoked in otherwise normal men or animals by overfunction of the thyroid or adrenal glands, by irritations of the central nervous system or by drugs, particularly by anesthetics. The outstanding characteristic of true diabetes is its permanency, in fact, reports of cure of diabetes mellitus are extremely rare and always doubtful. The significance of

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1 Young, F G Permanent Experimental Diabetes Produced by Pituitary (Anterior Lobe) Injections, *Lancet* **2** 372-374 (Aug 14) 1937, The Diabetogenic Action of Crude Anterior Pituitary Extracts, *Biochem J* **32** 513-523 (March) 1938

2 Evans, cited by Young<sup>1</sup>

3 Houssay, cited by Young<sup>1</sup>

the contribution of Young is that for the first time since the epoch-making discovery of von Mering and Minkowski<sup>4</sup> (1889) diabetes has been produced experimentally which conforms to clinical diabetes in its primary characteristic, namely, *permanency*.

Unsatisfactory results were obtained by Young in many experiments with mice, rats, guinea pigs, rabbits and cats, but with dogs and comparably large amounts of material the effects were unmistakable. Corresponding injections, for control, of extracts of muscle, liver and denatured pituitary substance gave completely negative results. Not all the dogs reacted equally, no result was obtained with 1 pregnant bitch, and only in 5 of the 6 dogs receiving suitable amounts of the extract were the diabetic manifestations lasting. The extracts were prepared from fresh pituitaries, frozen immediately in solid carbon dioxide and dissected in the frozen state. The anterior lobes were minced while still frozen, were ground with sand and ice-cold salt solution (2 cc per gram of pituitary) and after standing one hour were centrifuged in the cold room. The supernatant solution was injected intraperitoneally, without further attempt at sterility than that provided by the continuous low temperature. Extracts mildly acid and those mildly basic were equally active. Extracts of acetone-desiccated glands were somewhat less potent.

The amounts of material required were enormous as appears from the following description of a typical experiment given by Young.

The daily intraperitoneal administration of 10 g equivalent of saline extract was begun on the first day of experiment, after an initial control period. Polyuria and ketonuria appeared on the 3rd day but the excretion of sugar did not begin until the 5th day of injection when the daily pituitary injection was increased to 15 g equivalent of extract. During the daily injection of 15 g equivalent of extract the glycosuria increased until the 7th day of injection after which it began to decrease, finally disappearing on the 11th day, at which time the urine had become free from ketone bodies. It is interesting to note that at this time the daily urine volume was still much above the pre-injection level. The phenomenon of the disappearance of the symptoms of diabetes, despite the continued daily administration of that dose of extract which induced the appearance of diabetes, has occurred in all animals showing a diabetic response, including species other than the dog. If the daily administration of 15 g equivalent of extract had continued from the 11th day onward it seems most improbable that glycosuria would have reappeared. Nevertheless when the daily dose was increased to 20 g equivalent, on the 11th day glycosuria and ketonuria reappeared to fall again to zero on the 16th day of injection.

It was clearly of interest to determine if a daily level of injection could be reached which was of sufficient magnitude to prevent the animal becoming resistant to the diabetogenic action of the extract. With this object the daily dose was increased to 25 g/day on the 16th day of injection. This resulted in the reap-

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<sup>4</sup> von Mering, J., and Minkowski, O. Diabetes mellitus nach Pankreas-  
extirpation, Arch f exper Path u Pharmacol 26 371-387, 1890.

pearance of glycosuria which rose to 130 g / day on the 21st day, thereafter declining to about 50 g / day without showing any tendency to diminish further. On the 24th day the ketonuria reached a high level, and on the 26th day the animal passed into a semicomatose condition. At this time the CO<sub>2</sub>-combining power of the blood was 29 vol % compared with the normal value for the dog of 40 vol %. Injections were stopped on this day and the ketonuria subsequently rapidly decreased, but the glycosuria persisted, and, 4 weeks after injections had ceased, reached 264 g / day.

The subsequent history of this animal has been described elsewhere (Young,<sup>1</sup> 1937). The observations of Young have been confirmed by Lukens,<sup>5</sup> of the University of Pennsylvania, and by Best,<sup>6</sup> of Toronto.

The histologic structure of the pancreas and other organs in 6 of the dogs has been fully described by Richardson, of the Department of Anatomy, University College, London, and Young.<sup>7</sup> Their summary follows:

1 The pancreatic islets of two dogs, killed during a period of daily injections of a diabetogenic anterior pituitary extract, showed cellular proliferation and hydropic degeneration in individual islet cells.

2 The pancreas of a dog, which had been diabetic for ten months after cessation of pituitary injections, and which probably died in diabetic coma, contained no detectable normal islet tissue. The islets were completely hyalinised. Pancreatic tissue was obtained from a second dog, which had been diabetic for nearly ten months after cessation of injections, by biopsy operation during a period of insulin therapy. There were some normal islets, but the majority showed varying grades of depletion of cytoplasmic granules in the beta cells. Only very few of the islet cells of this dog exhibited hydropic degeneration.

3 One dog, the only one in six which failed to become permanently diabetic following treatment with suitable anterior pituitary extracts, had, one month after the cessation of pituitary injections, islets of Langerhans which appeared to be normal in every respect.

4 It seems possible that there are three types of response of the islet cells to the injections of anterior pituitary extract: (a) proliferation, (b) hydropic degeneration of some beta cells, (c) disappearance of the granules in the cytoplasm of other beta cells. Hyalinisation may finally occur. Hydropic degeneration was not a prominent feature of the islets of the two permanently diabetic dogs.

5 Proliferation of the islet cells, which was also observed in the pancreas of the rat (Richardson and Young, 1937) may precede, in the dog, the exhaustive or degenerative changes which accompany the onset of permanent diabetes.

6 The other endocrine organs of those dogs in which they were examined showed no striking histological changes.

One of us (Wilder) was shown the sections of the pancreas of 1 of Lukens' dogs that had died of peritonitis. The infection resulted

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5 Lukens. Personal communication to the authors.

6 Campbell, J, and Best, C. H. Production of Diabetes in Dogs by Anterior-Pituitary Extracts, *Lancet* **1** 1444-1445 (June 25) 1938.

7 Richardson, K. C, and Young, F. G. Histology of Diabetes Induced in Dogs by Injection of Anterior-Pituitary Extracts, *Lancet* **1** 1098-1101 (May 14) 1938.

from repeated injections of unsterilized extract before severe diabetes had developed. These sections revealed what was interpreted as hyperplasia, as well as hydropic degeneration of the insular epithelium.

In the experiment described by Best<sup>6</sup> the dog continued to excrete sugar for fifty-eight days after injections were discontinued, removal of the pancreas at the end of this time had little effect on the animal's requirement for insulin. In this pancreas the islands of Langerhans showed extreme hydropic degeneration. Furthermore, an assay of the organ revealed a low content of insulin.

The most likely interpretation of these findings is one which harmonizes fully with the unitary hypothesis of diabetes, namely, that the action of the secretion of the anterior lobe of the pituitary is antagonistic to insulin and that a balanced output of this secretion of the pituitary and of insulin is normally maintained by the respective glands of origin, so that if one gland oversecretes, the other in consequence is driven to greater activity. The insular epithelium of the pancreas normally possesses a reserve capacity sufficient to meet all ordinary and almost all extraordinary demands, but that it can be exhausted, if driven to extremes, with resulting hydropic degeneration followed by atrophy, was clearly shown by F. M. Allen's<sup>8</sup> observation of hydropic degeneration and atrophy of the islands in the remnants of pancreas left after partial pancreatectomy. When dogs are deprived of more than nine tenths of the pancreas, the remaining insular tissue, since the tail of the pancreas contains much more insular epithelium than the head and only a part of the head is left, represents much less than a tenth of the original insular epithelium. In such animals heavy feeding (of sugar) causes hydropic degeneration of the island cells and progressively intensifying diabetes. When the pancreas is intact and possessed of its usual reserve, neither hydropic degeneration nor diabetes results from feeding sugar or even from continuous injections of large amounts of dextrose for days and weeks (unpublished observations). Nor did the injection of pituitary extract, in the enormous doses given by Young, push to extremes the pancreatic reserve of the mice, rats, guinea pigs, rabbits, cats and 1 of the dogs. In many of his dogs it did, as was evidenced, and in a few dogs extreme insular degeneration (hydropic) with consequent atrophy was produced, resulting in lasting diabetes. Thus only by exhausting the pancreas does the anterior lobe of the pituitary cause diabetes, and since in clinical diabetes there is no reason to suppose that the pituitary ever could supply amounts of its secretion comparable to the gigantic doses of extract (representing the glands of

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<sup>8</sup> Allen, F. M. Experimental Studies in Diabetes (Series III). The Pathology of Diabetes. I. Hydropic Degeneration of Islands of Langerhans After Partial Pancreatectomy, *J. Metab. Research* 1: 5-41 (Jan.) 1922.

25 oxen) given daily by Young, there is every reason to suppose that a primary defect of the pancreas must preexist in those few cases of diabetes in which pituitary overactivity legitimately can be suspected (acromegaly, menopause). If this explanation proves to be correct, it will be necessary to return to the point of view that a few, mostly clinicians, have never abandoned, namely, that some defect of the insular epithelium is requisite to the development of true diabetes mellitus.

*The Pituitary in Clinical Diabetes*—Davidoff<sup>9</sup> found frank diabetes in 12 of 100 of Cushing's cases of acromegaly. A later follow-up study of 150 of Cushing's cases by Root<sup>10</sup> revealed a slightly higher incidence. Our own experience, recently reviewed (unpublished), shows in 218 cases of acromegaly a maximum incidence of diabetes of 9.2 per cent (20 cases). The figure probably is high. In 3 instances the diagnosis of acromegaly was doubtful, and in 3 others the diabetes amounted to only an alimentary glycosuria. If these cases are excluded the incidence was only 6.4 per cent. This is not impressive, particularly in view of the fact that the onset of the diabetes in an indeterminate number of the cases certainly preceded that of acromegaly. The figure is scarcely higher than that found for diabetic patients of the same age groups with adenomatous goiter with hyperthyroidism.

In many of these 218 cases of acromegaly the process undoubtedly was burned out before the patient came for examination, and glycosuria of sufficient intensity to be interpreted as diabetes might have existed in a previous more active stage of hyperpituitarism. It is questionable, however, whether diabetes characterized by such impermanence deserves to be called diabetes mellitus. In other cases diabetes may have developed since examination, but the same could be expected in any group of nondiabetic patients and particularly in a group, such as this, containing many patients with elevation of the basal metabolic rate.

In this connection it is important also to note that nonacromegalic tumors of the hypophysis may provoke glycosuria by pressure on or invasion of the subthalamic region of the brain. Colwell,<sup>11</sup> even after an incomplete survey, found 38 cases in which nonacromegalic lesions of or near the hypophysis were accompanied by glycosuria or diabetes, and he suggested that this number compared favorably with the incidence of glycosuria and diabetes in patients with acromegaly. Looked at the other way, the incidence of acromegaly in the diabetic patients at the Mayo Clinic has been less than 0.3 per cent, representing not more than 1 acromegalic patient among every 469 diabetic patients.

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9 Davidoff, L. M. Studies in Acromegaly. III. The Anamnesis and Symptomatology in One Hundred Cases, *Endocrinology* **10** 461-483 (Sept.-Oct.) 1926.

10 Root. Personal communication to the authors.

11 Colwell, A. R. The Relation of the Hypophysis to Diabetes Mellitus, *Medicine* **6** 1-39 (Feb.) 1927.

It is often stated that diabetes associated with acromegaly runs an irregular course, but Colwell, in his critical review of the literature, did not find it so, and in our more recent experience as well as in our earlier experience, reported by Yater,<sup>12</sup> acromegalic patients with severe diabetes have responded to dietetic management and insulin in no unusual way. However, Berg,<sup>13</sup> in a study of the reaction to dextrose tolerance tests and to insulin in 6 cases in which there were the characteristic features of acromegaly, found 3 in which the extent of the lowering of the blood sugar content by insulin was much less than normal, and in these cases the blood sugar curves were of the diabetic type. Since the findings in the other 3 cases were not abnormal, he concluded that the "anti-insulin factor" of the pituitary may or may not be involved in the presence of adenomas affecting the growth factor. Mauriac and Broustet,<sup>14</sup> in their study of a patient in whom symptoms of diabetes and those of acromegaly developed simultaneously, found the diabetes at first to be perfectly amenable to treatment with not more than 40 units of insulin, although later, after roentgen irradiation of the region of the pituitary, 80 to 120 units was needed for control. Also, Flaum,<sup>15</sup> giving insulin and dextrose simultaneously to patients with insulin-sensitive diabetes and to 2 patients with acromegaly and diabetes, obtained evidence of insulin insensitivity in the latter group. Thus some degree of insensitivity to insulin is to be found in some but not all cases of acromegalic diabetes, however, severe insulin resistance in such cases has not been reported, and in all instances of marked insulin resistance, such as occurred in a case reported by Marble,<sup>16</sup> attempts to demonstrate the responsibility of the pituitary have failed.

There is ground for the suspicion that the functional overactivity of the anterior lobe of the pituitary is in part responsible for the unusual frequency of diabetes in older women. However Pijoan and Zollinger<sup>17</sup>

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12 Yater, W. M. Acromegaly and Diabetes. Report of Six Cases, *Arch Int Med* **41** 883-912 (June) 1928.

13 Berg, B. N. Insulin Response in Acromegaly, *Bull Neurol Inst New York* **6** 178-182 (Aug.) 1937.

14 Mauriac, P., Broustet, P., Saric, R., and de Lachaud, R. Insulinorésistance et radiothérapie dans le diabète acroméganique, *Progres méd*, March 19, 1938, pp 413-421.

15 Flaum, G. Insulin-Insensitivity. Its Possible Relation to the Pituitary Gland, *Endocrinology* **23** 630-636 (Nov.) 1938.

16 Marble, A. Insulin Resistance. Report of a Case of Marked Insensitivity of Long Duration Without Demonstrable Cause, *Arch Int Med* **62**:432-446 (Sept.) 1938.

17 Pijoan, M., and Zollinger, R. Observations on Carbohydrate Metabolism Following Irradiation of the Pituitary Gland, *Endocrinology* **21** 357-360 (May) 1937.

could obtain no evidence of abnormality of carbohydrate metabolism in a group of 20 otherwise normal women who were subjected to 1,200 to 1,600 roentgens of radiation to the pituitary for the treatment of the menopausal syndrome. Thirty-five per cent had a definite and sustained decrease in the number of flashes, but the blood sugar curves, which in all cases were normal before irradiation, remained so afterward, the sensitivity to insulin was unaltered, and in an isolated examination the rise of the respiratory quotient after the oral administration of dextrose was unchanged.

*The Adrenal Gland and Diabetes*—That abnormally mild diabetes follows pancreatectomy in animals when the pituitary also has been removed (the Houssay animal) has now become general knowledge. Reference was made in a previous review<sup>18</sup> (1937) to the cats of Long and Lukens that showed similar amelioration of pancreatectomy diabetes after bilateral adrenalectomy. The two operations, hypophysectomy and bilateral adrenalectomy, seemed to have the same effect, except that the diabetes of the Houssay animal could be greatly intensified by injection of anterior pituitary extract, whereas injecting extracts of adrenal cortex into the cats of Long<sup>19</sup> and Lukens<sup>20</sup> was without any such result. The failure to obtain an increase in the manifestations of diabetes in their animals was puzzling, because much evidence suggested that the ameliorating effect of hypophysectomy in diabetes following pancreatectomy was related to the atrophy of the adrenal cortices which follows that operation. The evidence included the fact that after the adrenals are removed from Houssay dogs, injections of anterior pituitary extract are no longer effective. This has been disputed by Houssay. In any case, positive diabetogenic results with injections of extracts of adrenal cortex were finally obtained by Lukens and Dohan,<sup>21</sup> and the explanations offered for the previous failures were the use of cats in the earlier experiments, an unfavorable species, and their meat diet, rich in potassium. Experiments with dogs showed that adrenal cortex extract is capable of restoring to a considerable extent the diabetes of the adrenalectomized, depancreatized animal.

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18 Wilder, R. M., and Wilbur, D. L. Diseases of Metabolism and Nutrition. Review of Certain Recent Contributions, *Arch. Int. Med.* **59** 329-364 (Feb.) 1937.

19 Long, C. N. H. The Influence of the Pituitary and Adrenal Glands upon Pancreatic Diabetes, *Medicine* **16** 215-247 (Sept.) 1937.

20 Lukens, cited by Long<sup>19</sup>.

21 Lukens, F. D. W., and Dohan, F. C. Further Observations on the Relation of the Adrenal Cortex to Experimental Diabetes, *Endocrinology* **22** 51-58 (Jan.) 1938.

In the meantime, Long, Fry and Thompson<sup>22</sup> have also obtained evidence of diabetogenic activity in cortical extract. They performed partial pancreatectomy on over 100 rats at an age of 25 to 30 days, and about 30 per cent of the animals later exhibited spontaneous glycosuria when fed. These later were adrenalectomized, and if salt was provided abundantly they could be kept in good health. After the adrenalectomy the glycosuria either disappeared or was greatly diminished. It then could be made to reappear or increase if adrenals of 1 day old rats were engrafted or if daily with the drinking water 5 to 10 cc of a potent cortical extract was administered. Of additional interest is the fact that it also could be made to reappear if 3 mg of either of the crystalline compounds A and B isolated from adrenal cortex by Kendall and supplied by him was administered *by mouth*. A comparable result was obtained when large quantities of either the extract or the crystalline compounds were given to partially depancreatized, but otherwise normal rats during fasting. Long also has reported that the extract and the crystalline compounds caused in normal rats a marked increase in the glycogen content of the liver and, in a few animals, slight hyperglycemia. The acetone body content of the liver increased, and a few experiments indicated an increase in urinary nitrogen.

Clinical evidence of a role of the adrenal cortex in carbohydrate metabolism is also available. A review of the literature by Duncan and Fetter<sup>23</sup> revealed 8 proved cases of adrenocortical tumor with diabetes, and Long<sup>24</sup> and Lukens<sup>25</sup> found evidence of some impairment of carbohydrate metabolism in half of 55 reported cases of this disease. Our own experience in cases of this type has been relatively large. It comprised, when reported recently by Kepler and Wilder,<sup>26</sup> 2 cases of diffuse hyperplasia of the adrenal cortices and 8 cases of tumor. The diagnoses were confirmed by operation or necropsy. Frank diabetes was present in both cases of diffuse hyperplasia and in 1 of the cases of tumor. In addition, dextrose tolerance tests gave abnormal responses in 2 of the cases of tumor. However, in the 2 cases of hyperplasia, necropsy revealed other involvement of the pancreas (abscess in 1 and carcinoma in the other), and for 2 of the 4 patients with tumor who

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22 Long, C. N. H., Fry, E. G., and Thompson, K. W. The Effect of Adrenalectomy and Adrenal Cortical Hormones upon Pancreatic Diabetes in the Rat, *Am J Physiol* **123** 130-131 (July) 1938.

23 Duncan, G. G., and Fetter, F. Suprarenal Tumor—Hirsutism—Diabetes, *M. Clin. North America* **18** 261-268 (July) 1934.

24 Long, C. N. H. Disturbances of the Endocrine Balance and Their Relation to Diseases of Metabolism, *Ann Int Med* **9** 1619-1627 (June) 1936.

25 Lukens, cited by Long<sup>24</sup>.

26 Kepler, E. J., and Wilder, R. M. Disturbances of Carbohydrate Metabolism Observed in Association with Tumors of the Adrenal Cortex, *Acta Med Scandinav (supp)* **90** 87-96, 1938.



were living more than one year after operation the fasting values for blood sugar obtained elsewhere were normal

#### THE LIVER AND CARBOHYDRATE METABOLISM

The dictum of Claude Bernard that "the normal blood sugar level is the result of a precise equilibrium between the processes of anabolism (sugar formation by the liver) and catabolism (sugar utilization by the tissues)" has been accepted generally although supported heretofore only by indirect evidence. It now is established for dogs, with data of quantitative significance. Soskin, Essex, Herrick and Mann<sup>27</sup> not only have determined the rate of total flow of blood through the liver of suitably prepared dogs but have measured the arterial and venous components of the total, using for the purpose the mostromuhrs, previously described by Baldes, Herrick and Essex<sup>28</sup>. The stromuhrs were arranged ingeniously so as to record the rate of flow in the hepatic veins and in the portal vein and by difference that in the hepatic artery. The output and intake of sugar by the liver were calculated by correlating the rates of blood flow per minute with determined contents of sugar in the inflowing or outflowing blood. Observations were made during control periods and after intravenous injections of dextrose. Secretion of sugar by the liver occurred in the control periods, whereas after dextrose was injected secretion invariably ceased and retention followed. In the protocols of one experiment the rate of secretion for thirty minutes averaged 18 mg per minute, the animal weighed 18.9 Kg and the liver 655 Gm. The maximum rate of retention after intravenous injections of dextrose was 85.5 mg per minute.

An observation the significance of which was not discussed was that the portal vein or the hepatic artery, in different animals, sometimes carried as much as 90 per cent or as little as 10 per cent of the total amount of blood entering the liver. Such large differences were the exception, but reciprocal variations frequently occurred during the course of an experiment without accompanying variation in the total outflow of blood from the hepatic veins. Also, there were no comments on the fact that the rate of secretion of sugar in the control period of the experiment for which protocols were given, before sugar was injected and at a time when the animal presumably was in a post-absorptive state, was so much less than the rate at which sugar has been shown to disappear from the blood in the hepatectomized dog. By

27 Soskin, S., Essex, H. E., Herrick, J. F., and Mann, F. C. The Mechanism of Regulation of the Blood Sugar by the Liver, *Am J Physiol* **124** 558-567 (Nov.) 1937

28 Baldes, E. J., Herrick, J. F., and Essex, H. E. A Modification in the Thermostromuhr Method of Measuring the Flow of Blood, *Proc Soc Exptl Biol & Med* **30** 1109-1111 (May) 1933

our calculation, as was stated, the rate of secretion in the control period averaged, for thirty minutes, 18 mg per minute. This represented only 57 mg per kilogram of body weight per hour, whereas in the liverless dog the rate of disappearance of sugar is close to 250 mg per kilogram per hour. Apparently it is unjustifiable to assume, as has been done, that the liver of the intact animal must always secrete sugar during fasting at the high rate of 250 mg per kilogram per hour to prevent hypoglycemia and to deduce therefrom that the amount of sugar derived from protein is insufficient to prevent the development of hypoglycemia in the intact animal. Even the much lower figure of 57 mg per kilogram per hour (representing 18 mg per minute in the control period of this recent experiment) may be erroneously high, since errors of  $\pm 2$  per cent are inherent in the clinical determination of the blood sugar content and a 10 per cent error is present in measurements of blood flow with the thermistomuh. Also, in this experiment the liver presumably was not nearly emptied of its glycogen.

#### HOMEOSTASIS OF BLOOD SUGAR

As mentioned in a previous review,<sup>29</sup> Soskin and his collaborators found that when the blood sugar value for depancreatized dogs was maintained at a normal level by constant intravenous injections of dextrose and insulin, added doses of dextrose gave normal blood sugar curves. Under the conditions of their experiments extra insulin to provide for the increased intake of dextrose was neither available nor required. The hypothesis that the maintenance of homeostasis of the blood sugar in the normal organism after ingestion of carbohydrate is dependent on the ability of the pancreas to secrete insulin was therefore held to be untenable. Ricketts<sup>30</sup> has challenged this conclusion. His experiments showed that protamine insulin in sufficient doses to hold the blood sugar value at normal levels during fasting would not prevent a hyperglycemic response to ingestion of carbohydrate in cases of severe diabetes or in depancreatized dogs. In cases of mild diabetes, in which supposedly the pancreas is not incapable of responding with secretion of "extra" insulin, the blood sugar curves after ingestion of dextrose were more nearly normal. Soskin and his collaborators postulated the necessity for an adequate supply of insulin but concluded that an extra supply at the time of ingestion of carbohydrate is unnecessary.<sup>29</sup> Ricketts pointed out that his different results probably were

29 Wilder, R. M., and Wilbur, D. L. Diseases of Metabolism and Nutrition. Review of Certain Recent Contributions, *Arch. Int. Med.* **57**: 422-471 (Feb.) 1936.

30 Ricketts, H. T. Carbohydrate Tolerance After Protamine Insulin. Its Bearing on the Physiology of Insulin Secretion. *J. Clin. Investigation* **17**: 795-801 (Nov.) 1938.

to be explained by differences in experimental procedure. Soskin and his associates were determining what the organism could be made to do under artificial conditions, on the other hand, what Ricketts was studying was what it actually does as a matter of everyday existence. That the homeostatic mechanism of the liver may play an independent part in regulation of the blood sugar is not denied, but in his opinion his experiments indicate that the proper functioning of the liver, under normal circumstances, depends on the availability of an extra supply of insulin at the time of ingestion of carbohydrate.

#### PATHOLOGY OF DIABETES <sup>31</sup>

A second edition of Warren's <sup>32</sup> now classic work entitled "The Pathology of Diabetes Mellitus" has been based on a larger experience with this subject than any one individual has ever before accumulated. The total number of necropsies on diabetic patients was 484. Nine were on children under 11 years of age, 29 were on older children and adolescents, and 8 were on patients with hemochromatosis. In addition, because, as Dr. Joslin has said in the foreword, the present diabetic patient is "half and half surgical," Dr. Warren has had the opportunity to study nearly as many biopsies as necropsies. "I am thankful," Dr. Joslin has added, "for the training which Dr. Warren received as editor of the volume of Preventive Medicine issued by the Harvard Medical School, because automatically a note of prevention of diabetes and its complications permeates the text." The motto on the wall of Dr. Warren's "modern operating room" betokens this sentiment—*Mortui vivos docent*.

The years that have passed since the publication of the first edition of this book have brought new problems to the attention of pathologists. Are infants of diabetic mothers abnormally large, with hyperplastic islands of Langerhans? What is the nature of the hepatomegaly in diabetic children? Why does arteriosclerosis in the diabetic patient tend to affect, selectively, the intrinsic arteries of the heart and the arteries of the leg? What part in clinical diabetes is played by the pituitary body? These and many other pressing questions have received consideration. Examination of the pituitary body by serial section in 18 cases of diabetes and of random sections of the pituitary body in 26 more cases revealed no constant significant abnormality. Vacuolation of the basophilic cells of the anterior lobe, comparable to that

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<sup>31</sup> The following review of Warren's book entitled "The Pathology of Diabetes Mellitus" was written for the section on book notices of *The Journal of The American Medical Association*.

<sup>32</sup> Warren, S. The Pathology of Diabetes Mellitus, ed. 2, Philadelphia, Lea & Febiger, 1938.

described by Kraus,<sup>33</sup> also was seen in control cases. The acidophils were normal in number except in 1 instance, adenomatous groups of cells, such as Kraus has stained, were not found.

The increase in size and weight of the liver in diabetes may be due to a variety of conditions and is not always associated with increased accumulation of fat. The content of fluid is important, study of some of the larger livers suggests hydrops of the cells rather than an excess of fat or glycogen. The abdominal pain not infrequently associated with hepatic enlargement in diabetes may result from stretching of the capsule, as suggested by Marble.<sup>34</sup> This implies rapid change of size, perhaps too rapid for deposition of fat, but quite compatible with fluctuation of intracellular fluid. However, at necropsy the total fatty acid in the liver of persons with diabetes was found to range from 4.1 to 10.8 per cent of the wet weight of fresh liver, whereas for persons without diabetes the range was from 2.2 to 4.5 per cent.

The following statements received from Dr. Warren provide a résumé of what he regards as the most significant contents of his book.

With nearly double the number of cases the frequency figures for various pathologic lesions remain substantially as they were in the first edition.

The histologic normality of the pancreas in one-fourth of the cases is confirmed, and thus gives hope of ultimate cure under favorable conditions.

The observations on the incidence of arteriosclerosis and its possible relationship to unbalanced diets have been amplified.

Topics receiving new consideration include ophthalmic pathology, hyperplasia of the island of Langerhans in the infants of diabetic mothers, and medico-legal aspects of diabetes.

Further evidence of regeneration of the pancreas in diabetes has been adduced.

The studies provide evidence that the newer insulins have no harmful effect in therapeutic doses and that the role of the pituitary and of the adrenals in human diabetes is minor.

His book is a compact mass of interesting material of this type. The illustrations are excellent, and the writing is concise and clear. It is to be highly recommended for all students of diabetes and pathology.

#### THE DIET IN DIABETES

Reference was made in an earlier review to the suggestion of Marks<sup>35</sup> that the anterior lobe of the pituitary may be stimulated by a diet inadequate in carbohydrate, thus accounting for impairment of tolerance for sugar and decreased sensitivity to insulin when the intake of starch and sugar is restricted. Himsworth and Scott<sup>36</sup> subsequently

33 Kraus, E. J., cited by Warren.<sup>32</sup>

34 Marble, cited by Warren.<sup>32</sup>

35 Marks, H. P., cited by Wilder and Wilbur.<sup>18</sup>

36 Himsworth, H. P., and Scott, D. B. M. The Relation of the Hypophysis to Changes in Sugar Tolerance and Insulin Sensitivity Induced by Changes of Diet, *J. Physiol.* **91** 447-458 (Jan.) 1938.

obtained other evidence to support this view. In hypophysectomized rabbits the sugar tolerance and insulin sensitivity were found to remain high, irrespective of whether the diet was low or high in carbohydrate, and when extract of the anterior lobe of the pituitary was injected into these animals while they were receiving high carbohydrate diets, impairment of tolerance and sensitivity to insulin occurred, similar to that observed when a low carbohydrate diet was given. It has been indicated, however, by Himswoorth that factors other than increased pituitary activity may also be concerned in the effect produced by low carbohydrate diets.

The epidemic of diets high in carbohydrate has not as yet invaded France. Labbé<sup>37</sup> has written critically of the observations of Porges and Adlersberg, advocates of these regimens. Examination of their report, he said, revealed that the same result, in the cases of moderately severe diabetes, would have been obtained more rapidly by another regimen, and in the other cases what was accomplished seemed to be attributable more to insulin than to the regimen. His own experience with the procedure of Porges and Adlersberg has not been favorable. Glycosuria and elevated blood sugar levels resulted. It is an illusion to depend on hyperglycemia provoked by the administration of carbohydrate to stimulate a secretion of insulin. This may be true for healthy men, it is not true for the diabetic patient. The hyperglycemia and glycosuria of diabetes are always a function of a supply of carbohydrate in excess of the capacity of the patient for its utilization.

Newburgh and some of his colleagues,<sup>38</sup> according to F. M. Allen, have merely rediscovered the value of undernutrition in their studies revealing marked gains in tolerance in originally obese diabetic patients whose weight had been rigidly reduced. According to Newburgh,<sup>38</sup> the hyperglycemia and glycosuria of middle-aged, obese patients are complications of obesity, the primary condition is a lessened ability to lay down glycogen, possibly due to deposition of fat in the liver. Study of the respiratory quotients of these patients gave no indication that the derangement was accompanied by a decreased capacity to oxidize dextrose, thereby setting this large group of glycosuric patients (44 per cent of all diabetic patients) apart, in the sense that their ability to utilize dextrose is dependent only on obesity and is corrected by reduction of weight. Allen<sup>39</sup> has maintained that reduction of weight

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37 Labbé, M. Les régimes pauvres en graisses et riches en hydrates de carbone dans le traitement du diabète, *Arch. d. mal. de l'app. digestif* **28** 209-222 (March) 1938.

38 Newburgh, L. H., Conn, J. W., Johnston, M. W., and Conn, E. S. A New Interpretation of Diabetes Mellitus in Obese, Middle-Aged Persons. Recovery Through Reduction of Weight, *Tr. A. Am. Physicians* **53** 245-257, 1938.

39 Allen, F. M., in discussion on Newburgh and others<sup>38</sup>

increases the tolerance in all cases of diabetes and that patients with inherently severe diabetes, in a sufficiently early or latent stage, will show carbohydrate combustion on a par with that of Newburgh's obese patients with mild diabetes. While we find ourselves in full agreement with Allen's interpretation, we nevertheless have profited from the emphasis placed by Newburgh and also by Fetter, Durkin and Duncan<sup>40</sup> on the advantage to be gained by lessening the weight of the obese diabetic patient. If body weight can be reduced to normal, the patient usually requires no insulin, and that this is the treatment of choice for obese diabetic patients is evident from the fact that the loss of weight is in itself desirable.

*Arteriosclerosis in Diabetes*—R. D. Lawrence,<sup>41</sup> of London, in a paper to which reference will again be made, expressed his belief that the danger of arteriosclerosis in diabetes has been exaggerated. He entirely disagrees with the current opinion that hypercholesteremia causes it or that a diet high in carbohydrate can prevent it. A clinical survey of 43 of his diabetic children, under treatment with insulin for ten or more years, revealed no evidence of vascular disease, as judged by blood pressure, retinal vessels and roentgenologic examination of the larger vessels, with 1 exception (retinal arteriosclerosis). Many of the children had been fed diets rather low in carbohydrate, in the majority the diabetic condition had seldom been perfectly controlled. The frequent occurrence of arterial occlusive changes is confined almost entirely to middle-aged and elderly diabetic patients who have mild diabetes and do not show marked hypercholesteremia. In these cases Lawrence suggested that a pituitary influence may be responsible. In this type of case relative insensitivity to insulin is found, and control with insulin can best be obtained with a diet low in calories and rather low in carbohydrate, rather than with larger amounts of carbohydrate and more insulin.

#### INSULIN

*Protamine and Other Long-Acting Insulins*—The literature contains an increasingly large number of articles dealing with protamine zinc insulin. For the most part these are repetitious, some are critical, but on the whole those coming from centers where experience in the treatment of diabetes is large confirm earlier reports of benefit. The use of protamine zinc insulin in Germany was delayed owing to the introduction at about the same time of "insulin durant," recommended by

40 Fetter, F., Durkin, J. K., and Duncan, G. G. Dietary Versus Insulin Treatment of the Obese Diabetic Patient, *Am J M Sc* **195** 781-787 (June) 1938.

41 Lawrence, R. D. The Treatment of Insulin Cases by One Daily Injection, *Acta med Scandinav (supp)* **90** 32-53, 1938.

Katsch<sup>42</sup> and Storrington<sup>43</sup> The action of this product is said to extend over two or three days. A disadvantage is the incorporation of the insulin in a mixture of lipoids, which necessitates injection intramuscularly with special syringes. A preparation with which Zirwer,<sup>44</sup> in Frankfurt, has been experimenting is "deposulin," a product of the Brunnengröber firm. This is a mixture of insulin and solution of posterior pituitary, the latter constituent by its vasoconstricting effects retarding absorption. Schweers<sup>45</sup> also has written about this preparation. Beckmann and Weitzsacker,<sup>46</sup> in Stuttgart, investigated simultaneously "deposulin" (Brunnengröber), "adrenalin-insulin-novo," "depotinsulin" (Bayer) and protamine zinc insulin and found the last two to be superior to the others and approximately equal to each other in effect. "Depotinsulin" (Bayer), also referred to by Umber and his associates,<sup>47</sup> is an insulin bound to (adsorbed by) a nonprotein colloid.

Confirmative of the results obtained with protamine zinc insulin by Danish, American and English investigators is a report by Falta,<sup>48</sup> of Vienna, who has recommended (1) early morning injection of protamine zinc insulin, (2) the giving of any supplementary ordinary insulin required before the noon meal, and (3) the administration of a small meal at bedtime. Likewise confirmative have been the observations of Taeger and Danish,<sup>49</sup> of Schuttenhelm's clinic in Munich, and those of Umber and his associates,<sup>50</sup> of Berlin. The experience of Umber has covered the use of protamine zinc insulin in 250 cases. However, he entertains some doubt as to the wisdom of adding a protein substance to insulin and has been endeavoring to obtain equal prolongation of the action of insulin by the use of nonprotein colloids.

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42 Katsch, G., Scholderer, H., and Klatt, K. Depotinsulin, *Ztschr. f. klin. Med.* **129** 608-626, 1936.

43 Storrington, cited by Katsch, G., and Klatt, K. Insulin-Depotbehandlung, *Med. Klin.* **1** 369-370 (March 12) 1937.

44 Zirwer, K. Beobachtungen über Insulindepotbehandlung, *Klin. Wchnschr.* **16** 1121-1122 (Aug. 7) 1937.

45 Schweers, A. Klinische Untersuchungen zur Behandlung des Diabetes mellitus mit Depotinsulin "Insugerman," *Klin. Wchnschr.* **16** 392-396 (March 13) 1937.

46 Beckmann, K., and Weitzsacker, J. Klinische Erfahrungen mit verschiedenen Depotinsulinen, *Klin. Wchnschr.* **17** 1321-1325 (Sept. 17) 1938.

47 Umber, F., Storrington, F. K., and Follmer, W. Erfolge mit einem neuartigen Depotinsulin ohne Protaminzusatz (Surfen-Insulin), *Klin. Wchnschr.* **17** 443-446 (March 26) 1938.

48 Falta, W. Ueber Protamin-Zink-Insulin, *Klin. Wchnschr.* **16** 1633-1639 (Nov. 20) 1937.

49 Taeger, H., and Danish, L. Klinische Erfahrungen mit Deposulin, *Klin. Wchnschr.* **16** 1639-1642 (Nov. 20) 1937.

50 Umber, F., Storrington, F. K., and Glet, E. Klinische und ambulante Erfahrungen mit verschiedenen Insulindepotpräparaten an 250 Diabetikern, *Klin. Wchnschr.* **17** 190-196 (Feb. 5) 1938.

Boller,<sup>51</sup> from Eppinger's clinic in Vienna, has described 2 fatal cases with autopsies in which death was attributed to overdosage with protamine zinc insulin. In one of these, metastatic carcinoma of the adrenal glands explained the absence of all antagonism to insulin, in the other case, nothing could be found to account for the fatality. In both cases, and in no others in which protamine zinc insulin was used, a soft, pitting edema of the legs developed a few days before death and disappeared shortly before death. This was the only untoward symptom and suggested that this type of edema may be regarded as a warning of dangerous hypoglycemia.

Somogyi<sup>52</sup> has been studying the pendulum-like fluctuations which normally occur in the blood sugar level after administration of dextrose. In dogs and man directly after the hypoglycemic phase of a blood sugar curve, secondary hyperglycemia frequently is encountered before the fasting level is reestablished. In diabetes the prevalence of hyperglycemia attests to dislocation of the normal enzymatic balance of liver glycogen  $\rightleftharpoons$  blood sugar, in the direction of blood sugar, and when to this the stimulating effect of hypoglycemia is added, the swing, compensatory to any hypoglycemia, may be grossly exaggerated. In a patient under treatment with insulin the glycosuria accompanying the upward swing of the blood sugar level may prompt the physician or patient to increase the dose of insulin, whereby the pendulum effect is further aggravated and results, in Somogyi's opinion, in aggravation of the diabetes. Bowcock and Wilkinson<sup>53</sup> also have been discussing this phenomenon. They have called it the insulin paradox, because under these circumstances increasing the dose of insulin may be ineffective in preventing glycosuria. We recently saw a patient who, because of the persistence of traces of sugar in diurnal specimens of urine, had gradually increased his doses of protamine zinc insulin from 15 to 80 units a day. Fortunately or unfortunately, he was resistant to most or the symptoms of insulin reaction, although he complained of dull headaches. We ordered an immediate reduction of the dose to 20 units, and although the same diet was consumed, the glycosuria, to the patient's great surprise, was immediately controlled.

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51 Boller, R., and Pilgerstorfer, W. Die Hypoglykämie bei Protamin-Zink-Insulinanwendung, *Klin Wchnschr* **17** 1065-1068 (July 30) 1938.

52 Somogyi, M. Hyperglycemic Response to Hypoglycemia in Diabetic and in Healthy Individuals, *Proc Soc Exper Biol & Med* **38** 51-55 (Feb) 1938.

53 Bowcock, H., and Wilkinson, C. Solution of Zinc-Insulin Crystals Versus Regular Insulin and Protamine Zinc Insulin, *J M A Georgia* **27** 351-355 (Sept) 1938. Bowcock, H. Solution of Zinc-Insulin Crystals—A New Therapeutic Agent. Comparison with Unmodified and Protamine-Zinc Insulin, *ibid* **27** 361-363 (Sept) 1938.



From England, in a volume entitled "Medical and Physiological Papers," happily dedicated to Dr H C Hagedorn, are articles on protamine zinc insulin by Lawrence<sup>41</sup> and Graham<sup>54</sup> Lawrence described more fully his method of administering protamine zinc insulin and ordinary insulin in one syringe The soluble insulin should be drawn into the syringe *first*, "as it does not matter if a trace of acid insulin from the needle enters the buffered protamine bottle, whereas the entry of alkaline material to the acid bottle may make the soluble insulin alkaline and inert by the end of the bottle" In the mixture some of the soluble insulin disappears (10 to 20 per cent), but his case reports indicate that irregularities of action from day to day are no more conspicuous than when the two insulins are injected into separate sites A stable preparation of protamine zinc insulin and soluble insulin in one bottle has the disadvantage that the fixed proportion is not the best for all patients

Even with this treatment it rarely is possible to keep the urine constantly free from sugar without risk of hypoglycemia However, Lawrence has permitted some glycosuria in practically all his cases and "has learned to reduce the insulin if all the urine tests are sugar-free for even one and certainly for two days" In his opinion, "if the patient never passes sugar after supper or before breakfast, the basal dose is too high and should be reduced, perhaps by 4 units, if he never passes sugar after breakfast the soluble insulin should be reduced" In the majority of cases, severe diabetes is kept under reasonable control with one dose of mixed insulin a day In very severe diabetes other arrangements have been necessary Variation of method to suit each individual case gives the best individual results, but "unfortunately intense personal study is not available for most cases and some simple and dogmatic method suitable for the majority must be preached" This apology applies also to the description of the procedure used in the Mayo Clinic,<sup>55</sup> which, except that the two types of insulin are not mixed in one syringe, is much like that described by Lawrence

The ideal in the use of insulin is to imitate the action of the normal pancreas This, as Lawrence<sup>56</sup> suggested, probably involves (1) a small continuous secretion of insulin, and (2) increased secretion after meals to deal with ingested carbohydrate No one type of insulin has been prepared which can imitate both aspects of natural function The slowly acting preparations provide well for the small continuous supply

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54 Graham, G The Use of a Mixture of Ordinary and Protamine Insulin, *Acta med Scandinav* (supp) 90 54-63, 1938

55 Wilder, R M A Primer for Diabetic Patients, ed 6, Philadelphia, W B Saunders Company, 1937

56 Lawrence, R D, and Archer, N Some Experiments with Protamine Insulinate, *Brit M J* 1 747-749 (April 11) 1936

required for controlling endogenous production of sugar, but if given in doses large enough also to control the glycosuria which follows meals, they will provoke hypoglycemia. For meeting the increased requirement after the taking of food, in all but relatively mild diabetes, additional supplementary insulin that acts more quickly is necessary.

Graham<sup>54</sup> likewise has found advantage in giving protamine zinc insulin and ordinary insulin together in one syringe. He too appreciates that some change probably takes place in the insulins when they are mixed, but since the same change occurs each day the effect, he has stated, is not so haphazard as it appears. Graham also has commented on the irregularity of control obtained in cases of severe diabetes but has found this to be no more marked with protamine zinc insulin than it is with ordinary insulin. Therefore, he has attributed it not so much to varying rates of absorption of insulin but to the disease, which one day causes a greater demand for insulin and another day a smaller one. Also, Graham, like many others, has come to believe that some hyperglycemia and glycosuria are preferable to the use of excessive doses of insulin, which, although not provoking typical hypoglycemic attacks, causes lack of energy, depression and headache. These symptoms may occur with a normal blood sugar value and may be completely relieved if the dose of insulin is reduced and the blood sugar value is allowed to rise.

*Oral Administration of Insulin*—Efforts to protect insulin from the action of the enzymes of the gastrointestinal tract so as to permit its administration by mouth in the treatment of diabetes heretofore have been unsuccessful. That insulin is able to pass the intestinal barrier has been shown, however, by numerous investigators, using isolated loops of bowel, and J. R. Murlin and his associates<sup>57</sup> have presented evidence of activity when insulin, in preparations containing hexylresorcinol, was given perorally to depancreatized dogs. Clinical results with a different preparation have now been reported by Lasch and Schonbrunner<sup>58</sup>. These writers have found that acid organic dyes, such as congo red and trypan red, will protect insulin from disintegration by pepsin and that individual basic dyes, among them malachite green and rhodamine, similarly will protect it against trypsin. The

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57 Daggs, R. G., Murlin, W. R., and Murlin, J. R. Effect of Hexylresorcinol upon Absorption of Insulin from the Gastro-Intestinal Tract of Dogs, *Am. J. Physiol.* **120** 744-749 (Dec.) 1937. Murlin, J. R., Young, L. E., and Phillips, W. A. New Results on the Absorption of Insulin from the Alimentary Tract, abstracted, *Science* **86** 412 (Nov. 5) 1937.

58 Lasch, F., and Schonbrunner, E. Experimentelle Untersuchungen über perorale Insulintherapie unter Beigabe organischer Farbstoffe, *Klin. Wchnschr.* **17** 1177-1180 (Aug. 20) 1938.

addition of saponin to insulin was found by Walton and Basset<sup>59</sup> to increase absorption in Thy fistulas, and with tablets containing saponin, typan red, malachite green and dry insulin Lasch and Schonbrunner have conducted experiments which gave impressive results. Clinical trial of this preparation has been obtained in several German clinics, among them Eppinger's clinic in Vienna. Forty diabetic patients were given the tablets for limited periods in amounts representing doses of insulin varying from 60 to 300 units daily. Data regarding 8 of these patients are included in the report. The disease in most of them was severe, necessitating for its control the use of 45 to 60 units of insulin injected subcutaneously. The equally effective oral doses of insulin were from two to four times as large. The necessary inclusion of saponin limits the usefulness of the preparation, and some doubt as to the safety of long-continued administration of the dyes named may be expressed. No serious side effects were observed from the doses used, but nausea, vomiting and diarrhea, referable exclusively to the amount of saponin, were encountered. Some patients proved to be more sensitive to the disturbing effects of saponin than others. Two patients, however, had been treated for six and 1 patient for eleven months without the development of any disagreeable symptoms. The report was conservative. The authors claimed to have shown conclusively that insulin is absorbed and active when given by mouth, according to the procedure described, but they reserved judgment as to the clinical usefulness of the preparation until it has received wider clinical trial.

*Sensitivity to Insulin*—In an earlier review<sup>15</sup> attention was called to the contradiction between the conclusions of MacBryde,<sup>60</sup> using a modification of the Radoslav<sup>61</sup> procedure as a means of determining sensitivity to insulin, and those of Himsworth<sup>62</sup>. The subject has received further study by Klatskin,<sup>63</sup> as well as by Burgert, Scott and Nadler<sup>64</sup>. Klatskin studied 50 patients with diabetes with respect to their response to a standard dose of insulin, and with the MacBryde-Radoslav procedure found wide variation in the percentage of fall of

59 Walton and Basset, cited by Lasch and Schonbrunner<sup>58</sup>

60 MacBryde, C. M. Response to Insulin as an Index to the Dietary Management of Diabetes, *J. Clin. Investigation* **15** 577-589 (Sept.) 1936

61 Radoslav, C. S. Ueber die Wirkung des Insulins auf den Blutzucker beim Menschen, *Wien Arch. f. inn. Med.* **8** 395-412 (July) 1924

62 Himsworth, H. P. Diabetes Mellitus. Its Differentiation into Insulin-Sensitive and Insulin-Insensitive Types, *Lancet* **1** 127-130 (Jan. 18) 1936

63 Klatskin, G. The Response of Diabetics to a Standard Test Dose of Insulin, *J. Clin. Investigation* **17** 745-750 (Nov.) 1938

64 Burgert, P., Scott, R., and Nadler, W. H. A Comparison of Tests for Insulin Sensitivity, *Proc. Central Soc. Clin. Research*, 1938, p. 23

the blood sugar value (between 30 and 85 per cent) However, no sharp cleavage was apparent between groups of patients, and no significant relation appeared between sensitivity to insulin and clinical characteristics or response to high carbohydrate diets Burgert and his associates applied the insulin tolerance test of MacBryde to 14 patients, who previously had been tested with regard to insulin sensitivity by the Himsworth procedure, and found no dependable correlation One patient was unmistakably insensitive by both the MacBryde and the Himsworth method, otherwise the correlation was extremely poor, and in individual cases reversibility of sensitivity seemed to occur The conclusion was reached that no justification exists at present for the classification of diabetes into types on the basis solely of sensitivity or insensitivity to insulin

#### PROGNOSIS IN DIABETES

Diabetes ranks with cancer, syphilis and tuberculosis as a problem worthy of attention by agencies of public health and others with interest in preventive medicine From the point of view of prevention it differs from tuberculosis and syphilis in that eradication of the cause of the disease offers greater difficulties, but in this respect it is no more discouraging than cancer However, from the point of view of what can be done to protect the affected person from resulting disabilities, the results obtainable in diabetes are far greater than those possible in cancer and represent as much as has been accomplished in syphilis or tuberculosis Cancer, comparatively, is a barren field for the investment of public and private funds, yet millions of dollars annually is expended on studies of cancer and programs for prevention of cancer

The untreated or poorly treated diabetic patient is not only a candidate for diabetic coma but is also predisposed to tuberculosis, to all other infections and to degenerative disorders of all kinds As a result invalidism overtakes him, usually early, and his life soon is ended But with proper management these hazards are greatly diminished or prevented, and a vigorous, effective man or woman is preserved The chief requirement for good results is precise knowledge by the patient of what he needs to do Today diabetic patients, trained in centers where special attention is paid to diabetes, who have had diabetes fifteen years or more are numbered in the thousands And of those who received their training in the George F Baker Clinic about 900 have attained a *normal* life expectancy Moreover, the diabetic physicians who have been patients in that clinic have exhibited a death rate lower than that of the other patients, affording the best example of the value of knowledge of the disease by the patient

What is needed to extend these advantages to the diabetic population at large is more centers for training patients, this, and also much more interest in diabetes on the part of physicians and public health agencies. Diabetes is not a disease requiring a specialist for its management, but it does demand more painstaking attention than many physicians are willing to devote in order adequately to train the patients. These comments are provoked by the illuminating pamphlet, "Advances in the Treatment of Diabetes," issued by the Metropolitan Life Insurance Company and the George F. Baker Clinic.<sup>65</sup> The charts and accompanying comment present a "statistical and clinical epitome of diabetes today." The statement needs amplifying, however. It ought to be followed by the clause "among trained diabetic patients." The charts are part of those that were exhibited at the 1938 meeting of the American Medical Association.

Life tables constructed by Dublin and Marks for diabetic patients treated by Joslin<sup>66</sup> and traced to 1929 reveal dramatically the strides toward normality that well trained diabetic patients have made. The tabulations were constructed by the methods customary in reviewing survivorship experience in insurance investigations. One of the tables is reproduced here. In it the figures for expectation of life by periods (Naunyn, Allen and Banting) of Joslin's patients are compared with the data for the general population of the "original registration states." Appreciable gains are apparent for every age and for both sexes. They are most marked, as was to be expected, in children. A 10 year old diabetic boy of the Naunyn era had an expectancy of only one year, compared with a normal expectancy of fifty-one years, but in the second part of the Banting period the expectancy reached thirty-three and one-fifth years.

Survival figures for patients seen after 1929 in the George F. Baker Clinic undoubtedly will reveal still greater progress, but it is not to be supposed that this represents the general situation. Comparable statistics are nowhere available, but other results probably are much less encouraging, as is illustrated by the shocking mortalities (table 2) reported from abroad and cited by von Ángyan and his associates.<sup>67</sup> Also Kestermann and Schuwicht<sup>68</sup> commented recently that in spite of

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65 This pamphlet is obtainable on request from either of the institutions named.

66 Joslin, E. P., Dublin, L. I., and Marks, H. H. Studies in Diabetes Mellitus. VI. Mortality and Longevity of Diabetics, *Am J M Sc* **195** 596-608 (May) 1938.

67 von Ángyan, J., Donhoffer, S., and Donhoffer-Mittag, M. Zur Prognose des Diabetes, *Ztschr f klin Med* **133** 466-473, 1938.

68 Kestermann, E., and Schuwicht, E. Die Lebensschicksale unserer in der letzten 10 Jahren behandelten Diabetiker, *Ztschr f klin Med* **133** 458-465, 1938.

insulin the length of life and the duration of the disease for diabetic patients who have died are not appreciably better than in the pre-insulin era, averaging not over six or seven years

### HEMOCHROMATOSIS

Mention must be made belatedly of the excellent monograph on hemochromatosis published in 1935 by Sheldon<sup>69</sup> The study was based on an intensive search of the literature and the compilation therefrom of data on 311 cases which could be accepted as genuine The disease

TABLE 1—*Comparison of Expectation of Life of Diabetic Patients and Persons in the General Population (Joslin, Dublin and Marks<sup>66</sup>)*

Sex, Age	Expectation of Life (Years)							
	Diabetic Patients, Naunyn Era	General Popu lation, 1910	Diabetic Patients, Allen Era	General Popu lation, 1919-1920	Diabetic Patients, Banting Era, First Part	General Popu lation, 1919-1920	Diabetic Patients, Banting Era, Second Part	General Popu lation, 1923-1931
Males								
10	11	51.3	28	52.8	10.8	52.8	33.2	54.5
30	4.5	34.9	6.5	36.5	16.3	36.5	23.1	36.9
50	8.0	20.4	8.6	21.4	11.2	21.4	12.9	20.8
Females								
10	1.5	53.6	2.4	53.8	17.8	53.8	30.2	57.1
30	3.7	37.0	6.0	37.6	17.4	37.6	22.4	39.3
50	8.0	21.7	10.5	22.3	13.4	22.3	13.6	22.7

TABLE 2—*Mortality Statistics Reported by von Angyan and His Associates<sup>67</sup>*

		Number of Cases	Deaths, Percentage
Reinwein and Markert	1924-1930	184	38
Grafe	1924-1930	130	43
Henkel	1924-1931	1,082	44
Meythaler and Jakobi	1924-1931	225	40
Buttner	1924-1931	221	48
von Angyan and associates	1926-1936	532	26

is rare, but not so rare as formerly was assumed Butt and Wilder<sup>70</sup> found that the diagnosis had been made in 30 cases at the Mayo Clinic in a period of fifteen and one-half years, the diagnosis in each instance was supported by microchemical examination of the skin In a family described by Lawrence<sup>71</sup> hemochromatosis was found in 2 brothers,

<sup>69</sup> Sheldon, J. H. Haemochromatosis, London, Oxford University Press, 1935

<sup>70</sup> Butt, H. R., and Wilder, R. M. Hemochromatosis Report of Thirty Cases in Which Diagnosis Was Made During Life Arch Path **26** 262-273 (July) 1938

<sup>71</sup> Lawrence, R. D. Haemochromatosis and Heredity, Lancet **2** 1055-1056 (Nov. 9) 1935

with 3 other brothers and the mother showing some signs of the disease. Several other instances of the occurrence of hemochromatosis in brothers were mentioned by Sheldon, and in the series of Butt and Wilder 1 patient had a brother with enlargement of the liver and cyanotic pigmentation. This suggestive evidence of a familial character is consistent with the conclusions reached by Sheldon, Dry<sup>72</sup> and others, that in order to account for the amount of iron retained the onset of the disease must be dated back thirty to fifty years from the time a diagnosis is made. Some inborn error of metabolism seems to be involved which expresses itself in an inability of cells to rid themselves of ferrous compounds no longer useful (Sheldon).

The prognosis in hemochromatosis has been materially improved since the availability of insulin made possible the control of associated diabetes. Lawrence,<sup>73</sup> after reviewing the course of the disease and the duration of life in 12 cases, commented on the improvement as follows:

No one could yet venture on a prognosis for any particular patient, but it is clear that death can be postponed and activity made normal for many years. As Sheldon suggests, it is likely that a liver death (cholaemia, cirrhosis and ascites) will replace diabetic coma. As regards the liver, I feel that of all forms of cirrhosis—a hard, very large liver—this is probably the best. Here no violent toxic background is present to kill the liver cells, but a slow mechanical cause, the deposition of an iron excess. This gives the liver time to hypertrophy and regenerate enough new cells to maintain full liver function. This can go on adequately for many years, how long no one knows. But no immediately gloomy prognosis is justified if the insulin treatment is successful. I see no reason to tell these patients that they have a fatal disease and think it best, if necessary, to say that their diabetes is complicated by a large liver. The intelligent ones should never hear the words “bronzed diabetes” or “haemochromatosis” when perusal of the older encyclopaedias must be unnecessarily depressing.

#### GLYCOGENOSIS (VON GIERKE'S DISEASE)

It has been supposed that the upper and middle segments of the thoracic portion of the spinal cord are involved in the glycogenic function of the liver. The same segments provide innervation for other organs (heart, thyroid, parathyroids and adrenals), which not infrequently are involved in glycogenosis. Neuteboom,<sup>74</sup> reporting an atypical case of

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72 Dry, T. J. Hemachromatosis. Its Relation to the Metabolism to Iron, *Proc. Staff Meet., Mayo Clin.* **8** 56-59 (Jan 25) 1933.

73 Lawrence, R. D. The Prognosis of Haemochromatosis, *Lancet* **2** 1171-1172 (Nov 14) 1936.

74 Neuteboom, J. J. Zur Kenntnis der Glykogenkrankheit (Hepatomegalia glycogenica. Von Gierke-Van Creveld, Cardiomegalia glycogenica. Pompe), *Klin. Wchnschr.* **17** 1437-1441 (Oct 8) 1938.

glycogenosis, referred to experimental production of glycogenosis in young rabbits. The implantation of small pieces of platinum between the right articular processes of the fifth and sixth thoracic vertebrae and between the left articular processes of the first and second thoracic vertebrae was followed in 1 animal by the development of an atypical form of glycogenosis, almost exactly like that of the clinical case described. In another animal, injury by a carefully directed blow to the dorsal processes of the second and sixth thoracic vertebrae diminished the sensitivity of the animal to epinephrine and increased the acetone content of the blood and the glycogen content of the liver. The observation is suggestive and warrants further study.

#### DIABETES INSIPIDUS

Von Hann has been given credit by Findley<sup>75</sup> for the first suggestion that diabetes insipidus cannot occur unless functioning tissue of the anterior lobe of the pituitary is present. It was based on the astute observation, in autopsies of patients, that lesions destructive of the pituitary were associated with diabetes only when functioning tissue of the anterior lobe was spared. Confirmatory experimental studies by others followed. Thus a state of normal water balance seems in part to depend on a balance between the diuretic property of the secretions of the anterior lobe and the antidiuretic action of the posterior lobe of the pituitary. In addition, it has been established experimentally that extracts of the anterior lobe which normally provoke transient diuresis fail to do so in thyroidectomized animals and that the polyuria which follows hypothalamic puncture is greatly diminished by thyroidectomy. On these and other observations is based the current "Hann-Richter-Ranson hypothesis"<sup>75</sup> that the thyrotropic principle of the anterior lobe of the pituitary has diuretic activity and that diabetes insipidus depends on hypopitressinemia in the presence of this diuretic principle of the anterior lobe.

Partly on the basis of this hypothesis and also because of suggestions that the thyroid, perhaps independently, exerts diuretic activity (the well known occasional diuretic efficiency of thyroid and an isolated clinical observation by Strauss<sup>76</sup> of recovery from diabetes insipidus following the onset of spontaneous myxedema), Findley resorted to total ablation of the thyroid in a case of diabetes insipidus. The results were not sufficiently good to lead him to recommend the procedure. The reduction in the volume of urine was no greater than that which could be obtained with a low salt diet, nevertheless, the operation definitely

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<sup>75</sup> Findley, T., Jr. Thyroid-Pituitary Relationship in Diabetes Insipidus, *Ann Int Med* **11** 701-713 (Nov.) 1937

<sup>76</sup> Strauss, L., cited by Findley<sup>75</sup>



increased the patient's reactivity to administered pitressin and diminished his diuretic response to sodium chloride

Reference also has been made by Findley to a report by McConnell<sup>77</sup> of striking amelioration of diabetes insipidus in a woman after removal of a thyroid adenoma. The fact that in her case polyuria was said to be uninfluenced by solution of posterior pituitary in any form suggested to Findley that McConnell's observations ought to be repeated on pitressin-resistant patients. Cutler's<sup>78</sup> results with thyroidectomy in diabetes insipidus apparently were not striking.

#### OBESITY

Personal clinical experience has led us to believe that a good many cases of obesity which commonly have been attributed to glandular disturbances are due in reality to lesions of the central nervous system.<sup>79</sup> Gill,<sup>80</sup> of the Middlesex Hospital, London, in a contribution to the collected papers dedicated to Hagedorn, and Evans,<sup>81</sup> of King's College London, have contributed recent reports of a number of cases of obesity related chronologically to acute diseases involving the brain. These reports supplement similar contributions of others to whom the authors have referred, such as those of Hall<sup>82</sup> (1924) and von Economo<sup>83</sup> (1931), who described obesity following encephalitis lethargica, Raab<sup>84</sup> (1931), who found cases in which obesity was related to postvaccinal encephalitis, and Gamna<sup>85</sup> (1931), Coburn<sup>86</sup> (1931) and Moncrieff<sup>87</sup> (1932), who commented on its occurrence after rheumatic chorea. Moncrieff's patients had a feminine type of fat deposit. A case of Gamna's was described as an example of the adiposogenital syndrome, and in 1 of Evans' cases the diagnosis previously had been pituitary obesity. Evans has pointed out that the growth of pubic hair in these cases suggests that hypopituitarism is not the active factor.

77 McConnell, A. A., cited by Findley<sup>75</sup>

78 Cutler, E. C., cited by Means, J. H. *The Thyroid and Its Diseases*, Philadelphia, J. B. Lippincott Company, 1937, p. 89

79 Wilder, R. M. Regulation of the Weight of the Body, *Internat. Clin.* **1** 30-41 (March) 1932

80 Gill, A. M. Unclassified Types of Obesity, *Acta med. Scandinav.* (supp.) **90** 257-268, 1938

81 Evans, P. R. Obesity Following Chorea, *Brit. J. Child Dis.* **34** 179-186 (July-Sept.) 1938

82 Hall, cited by Gill<sup>80</sup>

83 von Economo, cited by Gill<sup>80</sup>

84 Raab, cited by Gill<sup>80</sup>

85 Gamna, cited by Gill<sup>80</sup>

86 Coburn, cited by Gill<sup>80</sup>

87 Moncrieff, cited by Gill<sup>80</sup>

Evans followed 27 patients with chorea, 2 patients were obese and 4 were gaining more rapidly than normal. The obesity began as the attacks of chorea were subsiding—after the first attack in 3 cases, after the second in 1 and after the third in 2. The chorea probably was rheumatic. In 2 cases it was associated with carditis, in 1 with polyarthritis and in others with rheumatic manifestations.

The cause of rheumatic chorea is uncertain, but encephalitis has been found in cases of acute chorea by Poynton and Holmes,<sup>88</sup> and the probability is entertained that obesity consequent to this disease is due to a lesion or lesions in the suprapituitary region of the diencephalon rather than in the pituitary. The treatment of obesity of the cerebral type, in our experience, is dietetic. If rigid control can be maintained the loss of weight can be predicted from the difference between the intake and the estimated total caloric requirement. The difficulty is with the appetite, which often is so grossly abnormal that the patient, like the diabetic patient of the era before insulin, is unable to resist the temptation to break his diet. This makes it extraordinarily difficult to secure his cooperation and to keep it long enough to accomplish all that is desired.

Since 1933 we have employed the very low caloric diet recommended for reduction of obesity by Evans and Strang.<sup>89</sup> Evans<sup>90</sup> now has reviewed his own results with the diet. Ours, with the method modified slightly to provide a more liberal supply of vitamins and minerals, have been very satisfactory.

#### GOUT

Talbott and Coombs,<sup>91</sup> at the annual meeting of the American Society for Clinical Investigation, reported on a study of values for uric acid in the serum in 68 nonaffected blood relatives of 16 patients with gout. All of these relatives were considered healthy, in none was a past history of acute arthritis obtained and all showed normal roentgenograms of the joints. Yet in 14 of these persons (21 per cent) the uric acid content of the blood serum was greater than the value which Talbott and his associates consider to be the upper limit for normal persons. Several of the persons with an elevated uric acid value were less than 30 years of age, which leads to the supposition that the metabolic abnormality begins at or shortly after birth and that it may exist throughout life without

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88 Poynton, F. J., and Holmes, G., cited by Evans.<sup>81</sup>

89 Evans, F. A., and Strang, J. M. The Treatment of Obesity with Low Caloric Diets, *J. A. M. A.* **97** 1063-1068 (Oct. 10) 1931.

90 Evans, F. A. Treatment of Obesity with Low-Calory Diets. Report of One Hundred and Twenty-One Additional Cases, *Tr. A. Am. Physicians* **53** 352-355, 1938.

91 Talbott, J. H., and Coombs, F. S. The Concentration of Serum Uric Acid in Nonaffected Members of Gouty Families, *J. Clin. Investigation* **17** 508 (July) 1938.

other symptoms. The data lend support to the hypothesis that gout is a familial disease and that one manifestation of it (elevation of the uric acid content of the serum) is subject to hereditary transmission.

The contention of Talbott that analysis for uric acid of *serum* (derived from blood allowed to clot under oil) furnishes more valid data than the customary procedure, in which whole blood is analyzed, is supported by additional data obtained in his laboratory and clinic by Jacobson.<sup>92</sup> In 177 examinations of 21 patients with gout the values ranged from 5.2 to 14.8 mg per hundred cubic centimeters of *serum*, with values exceeding 6.0 mg in 98 per cent. For 97 of 100 nongouty persons the values were below 6.0 mg. This is the best evidence of the diagnostic reliability of the value for uric acid yet presented, however, the number of patients examined was small, and the experience of Hench,<sup>93</sup> who has seen annually from 200 to 250 patients, nearly half of them with tophaceous gout, is not corroborative. Jacobson found that high serum values for uric acid were little influenced by a purine-free diet, which also is contrary to the experience of Hench and Slocumb.<sup>94</sup> It is important to emphasize that values for uric acid obtained for blood serum are consistently higher by 1 or 2 mg than those for whole blood and that the value of 6 mg per hundred cubic centimeters, set by Talbott and Jacobson, represents about 4.5 mg for whole blood. Also, until more evidence is presented it will continue to be unjustifiable to base a negative diagnosis of gout on values for uric acid of 4.5 mg for whole blood or 6 mg for blood serum. The day is long past when all arthritis went by the name of gout, today the large majority of mistakes in the diagnosis of gout, as Hench<sup>95</sup> repeatedly has emphasized, are failures to recognize gout when gout exists. The fault, he thinks, lies less with the individual physician than with the contemporary American medical thought, which has led physicians to believe that gout is either an extinct or a rare disease. In 40 per cent or more of the cases in which gout is not recognized it is tophaceous. In the others the diagnosis must be stated as "presumptive gout" or "pre-tophaceous gout," although in many of these cases deeply placed tophi probably escape detection. The report of such a case, in which, incidentally, the uric acid value of the blood serum varied, with the medication given, from 3.8 to 7.14 mg per hundred cubic centimeters, was made

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92 Jacobson, B. M. Uric Acid in the Serum of Gouty and Nongouty Individuals. Its Determination by Folin's Recent Method and Its Significance in the Diagnosis of Gout, *Ann Int Med* **11** 1277-1295 (Jan) 1938.

93 Hench, P. S. Personal communication to the authors.

94 Hench, P. S., and Slocumb, C. H. Personal communication to the authors.

95 Hench, P. S. The Diagnosis of Gout and Gouty Arthritis, *J Lab & Clin Med* **22** 48-53 (Oct) 1936.

by Rutledge and Bedard<sup>96</sup> In the discussion of this case the following criteria for the recognition of gout, as previously emphasized by Hench,<sup>97</sup> were given detailed consideration

1 Relatively trivial trauma may provoke an attack of gout the severity of which is out of proportion to the trauma

2 The dietary indiscretions (food, drink) of holidays, Thanksgiving, Christmas New Year's Day, the Passover, a birthday and lodge-nights, frequently provoke attacks

3 A useful maxim is "acute postoperative arthritis occurring within the first six days after an operation is generally gout"

4 The trauma, exposure and the dietary excesses of fishing, hunting and vacation trips are common incitants

5 An acute attack of gouty arthritis frequently may be precipitated in the course of treatment of gout-susceptible patients for coincident disease, namely, by liver therapy for pernicious anemia, by a ketogenic diet for bacilluria, by salyrgan or other diuretics given for dropsy, by ergotamine tartrate (gynergen) administered for migraine, or rarely by insulin for diabetes

6 A gouty patient with coincident polycythemia or leukemia is particularly prone to marked activity of his gout

7 About 98 per cent of patients who have gout are men

8 The first attack of gout occurs most frequently in patients who are thirty-five years or more of age Gouty arthritis is the most common form of acute arthritis to affect men aged more than forty years and gout should be thought of first when attacks of arthritis appear in a man of this age if gonorrhea and acute trauma have been excluded

9 The incidence of attacks of gouty arthritis is greatest in spring and fall although they may occur in any month

10 While an attack may come on at any time during the day or night, it is especially prone to occur between 2 and 7 a m

11 The speed of onset and development of an attack are usually rapid In no other form of arthritis does maximal disability develop as rapidly as in gout The maximal pain and swelling always are reached within thirty-six hours of the onset of any attack

12 The pain of gout may be moderate or severe, it is often "the worst ever" experienced by the victim

13 From one to two or more joints are involved The joints of the great toes are usually involved, those of the torso almost never Podagra or involvement of the big toes is not a sine qua non of gouty arthritis However, as Hench has noted elsewhere podagra is present in approximately 60 per cent of attacks

14 When the great toes are involved the maximal tenderness is generally on the mesial aspect of the metatarsophalangeal joint

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96 Rutledge, D I, and Bedard, R E Criteria for the Diagnosis of Presumptive (Pretophaceous) Gout Management of an Illustrative Case, Proc Staff Meet, Mayo Clin 12 149-156 (March 10) 1937

97 Hench, P S The Diagnosis of Gout and Gouty Arthritis, Proc Staff Meet, Mayo Clin 11 476-480 (July 22) 1936

15 The affected foot is not rather cold and bluish-white as in atrophic arthritis but warm and bluish-red, the skin is often shiny, edema and later desquamation of skin are commonly noted

16 Attacks are usually of relatively short duration varying from seven to twenty-one days

17 The tendency to full restitution of articular function is notable and for a long time the remissions are complete

18 Olecranon bursitis is common in gout

19 Attacks of renal colic or nephritis not uncommonly develop in cases of gout

An observation of some interest and possible therapeutic significance in gout was reported by Rosenberg,<sup>98</sup> namely, that large doses of insulin administered in the treatment of schizophrenia (9 observations, 3 patients) caused a marked fall in the concentration of uric acid in the blood. The fall was independent of clinical manifestations and occurred even when hypoglycemia was prevented by repeated administration of sugar (7 additional observations, 6 patients). The degree of depression varied on different days for the same patient as well as with different patients from 6.4 to 68.5 per cent, but in 10 of 16 observations it exceeded 25 per cent.

#### ALKAPTONURIA, OCHRONOSIS AND TYROSINOSIS

The urine in alkaptonuria contains homogentisic acid, an intermediate metabolite of tyrosine. A related condition was described in 1932 by Medes<sup>99</sup> and named tyrosinosis. In it tyrosine is not metabolized beyond the stage of parahydroxyphenylpyruvic acid. The urine of a patient described by her had reducing properties and also gave a positive Millon reaction. A search for other cases was made without success by Blatherwick.<sup>100</sup> His results revealed the extreme rarity of the condition, since he found not 1 instance in 26 000 examinations. A typical case of alkaptonuria with ochronosis was reported recently by Seaborn.<sup>101</sup> The patient was a man 70 years of age, with a history of urine which had stained his clothing from childhood and of recent arthritic pains and stiffness in many joints. The cartilages of the nose and ears and those of the knuckles were dark. Specimens of urine of 135 descendants in the direct line and 71 descendants of cousins of the patient were examined.

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98 Rosenberg, E. F. Effect of Insulin on the Concentration of Uric Acid in the Blood, *J Clin Investigation* **17** 233-235 (May) 1938

99 Medes, G. A New Error of Tyrosine Metabolism. Tyrosinosis, the Intermediary Metabolism of Tyrosine and Phenylalanine, *Biochem J* **26** 917-940, 1932

100 Blatherwick, N. R. Tyrosinosis. A Search for Additional Cases, *J A M A* **103** 1933 (Dec 22) 1934

101 Seaborn, E. A Case of Ochronosis, *J A M A* **110** 576-577 (Feb 19) 1938

at the Institute of Public Health of London, Canada, and in no other specimen than that of the patient was homogentisic acid found. The case is of special interest because of the long history obtained and the number of relatives examined.

#### BENCE JONES PROTEINURIA

The subject of Bence Jones proteinuria was given attention in this journal by Meyler,<sup>102</sup> who reported detecting Bence Jones protein regularly in normal calf bone marrow, as well as in the pus of abscesses of empyema and in the leukocytes of leukemic blood. The differences in the degree of proteinuria in cases of multiple myeloma as compared with that in leukemia and empyema were attributed to production of the protein in myeloma at a rate greater than the rate at which it normally is metabolized.

#### ACIDOSIS AND ALKALOSIS

The subject of acid-base balance, although allotted to the section on diseases of metabolism in the textbooks of medicine, involves so many fields of medicine that it never has been possible in this annual review of diseases of metabolism to give it the broad consideration it should receive. This year, however, reference can be made to a valuable general review of the subject by Sendroy.<sup>103</sup> The article covers points of importance and interest that have developed since the publication of the monograph by Peters.<sup>104</sup> In the article, incidental reference is made to the advocacy by Korányi and Szent-Györgyi<sup>105</sup> of succinic acid to combat ketosis in diabetic acidosis. Confirmation of their work has not to our knowledge appeared, but the important positions in medicine and biochemistry which these investigators occupy undoubtedly will lead others to consider their suggestion. Krebs,<sup>106</sup> on purely theoretic grounds, has suggested that citric acid should be more effective.

## II NUTRITION

BY DR WILBUR

Advances in nutrition during the past year which may be of particular interest to clinicians have had to do chiefly with the vitamins. Information on this subject is being added so rapidly that it is impossible for

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102 Meyler, L. Bence-Jones' Proteinuria, *Arch Int Med* **57** 708-713 (April) 1936.

103 Sendroy, J., Jr. Acid-Base Metabolism, in Luck, J. M. *Annual Review of Biochemistry*, Stanford University, Calif., Stanford University Press, 1938, vol. 7, pp. 231-252.

104 Peters, J. P. *Body Water*, Springfield, Ill., Charles C. Thomas, Publisher, 1935.

105 Korányi, A., and von Szent-Györgyi, A. Ueber die Bernsteinsäurebehandlung diabetischer Azidose, *Deutsche med Wchnschr* **2** 1029-1033 (July 2) 1937.

106 Krebs, H. A., cited by Sendroy.<sup>103</sup>

any one individual to keep in touch with the progress that is being made in this field of nutrition

The discovery during recent months of the marked therapeutic effect of nicotinic acid in cases of pellagra has been an event of outstanding interest to clinicians. Of almost equal interest have been advances made in various biologic and chemical procedures devised for the detection of vitamin deficiency states of mild and "preclinical" character. Much of the information which is now available regarding these problems and those having to do with the chemistry, physiology, pathology and other clinical phases of the vitamins has been reviewed in a series of articles published during the year in *The Journal of the American Medical Association*.

#### VITAMIN A

*Chemistry and Physiology*—Little information of value to clinicians has been added to the knowledge of the chemistry of vitamin A in the past year. The relation of this substance to its precursor carotene, the yellow pigment of plants, has been amply confirmed, as has the fact that conversion of carotene to vitamin A occurs in the liver. It has been suggested that this conversion occurs by means of an enzyme which has been called carotenase. In a recent review of the chemistry of vitamin A Palmer<sup>107</sup> pointed out that this vitamin is the only one so far discovered which is a product solely of animal metabolism from precursors which are metabolic products of plants only. There has been some evidence to indicate that vitamin A performs its function in chemical combination with other substances rather than as a free substance. This is attested to by the observations that the vitamin is absorbed as a bile acid compound, transported in the blood and lymph as a fat acid ester and stored in the liver as a similar compound. There also seems to be a close chemical relation between a protein vitamin A compound and the visual purple of the retina.

The indispensability of vitamin A for the normal functioning of epithelial cells has been recognized as the basis for the essential pathologic changes in vitamin A deficiency. Wolbach<sup>108</sup> considers that vitamin A may be a structural material which may be solely concerned in maintaining an apparatus within cells and not in the chemical processes proper for which the apparatus is necessary. If this conclusion proves to be true it seems logical, as Booher<sup>109</sup> has suggested, that the vitamin A

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107 Palmer, L. A. The Chemistry of Vitamin A and Substances Having a Vitamin A Effect, *J. A. M. A.* **110** 1748-1751 (May 21) 1938.

108 Wolbach, S. B. Vitamin Deficiency Experimentation as a Research Method in Biology, *Science* **86** 569-576 (Dec. 24) 1937.

109 Booher, L. E. Vitamin A Requirements and Practical Recommendation for Vitamin A Intake, *J. A. M. A.* **110** 1920-1925 (June 4) 1938.

requirement should bear a definite relation to body weight rather than to energy metabolism

The close chemical and physiologic relation of vitamin A to the pigment visual purple and therefore to the clinical manifestation night blindness has been recognized for several years. Recent observations reported by Hecht and Mandelbaum<sup>110</sup> indicate that just as vitamin A enters into the chemical cycle of the rod cells of the retina, owing to its association with visual purple, so it enters into the chemical cycle of cone cells, and that the sensitive substance of the cone cells, iodopsin or visual violet, is likely a conjugated carotenoid protein.

*Vitamin A Requirement of Man*—The daily requirement of vitamin A is still unknown. The uncertainty of the requirement of man for this substance lies in the fact that there is wide variability in minimal and optimal requirements and in absorption, storage, utilization and destruction of the vitamin and that there is not complete agreement as to the standard which should be established as a measure of vitamin A sufficiency. Booher,<sup>109</sup> who has recently reviewed the literature in regard to this problem, concludes that about 1,400 to 2,000 U S P units of vitamin A daily for an adult weighing 70 Kg suffices for the support of normal visual adaptation. It was suggested that the daily intake of vitamin A per kilogram of body weight of adults required for the prevention of night blindness (20 to 30 U S P units per kilogram) might be nearly a constant for vertebrate animals generally. Allowing a 50 per cent margin of safety for the maintenance of a moderate storage of vitamin A in the body, a total of about 3,000 U S P units of vitamin A daily has been suggested by Booher<sup>109</sup> for the normal adult. Provision of 6,000 to 8,000 U S P units of the vitamin for growing children and of at least 5,000 U S P units for pregnant and lactating women would presumably be adequate. The latter amount would be that contained in 1 quart (1 liter) of fresh whole milk, one egg, 1 ounce (28 Gm) of cheese, an average serving of a green leafy vegetable and 1 teaspoonful of cod liver oil daily.

Somewhat lower values for the minimal daily requirement of vitamin A were suggested by Edmund and Clemmesen,<sup>111</sup> who studied a group of prisoners by means of dark adaptation tests and concluded that a diet containing 1,370 U S P units daily was adequate to obliterate seasonal oscillations in power of distinction and that therefore this amount is necessary for an adult.

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110 Hecht, S., and Mandelbaum, J. Rod-Cone Dark Adaptation and Vitamin A, *Science* **88** 219-221 (Sept 2) 1938.

111 Edmund, C., and Clemmesen, S. On Deficiency of A Vitamin and Visual Dysadaptation II, London, Oxford University Press, 1937, pp 1-77.



*The Effects of Vitamin A Deficiency on Certain Organs*—Clinicians in this country who are interested in deficiency states read much concerning the cutaneous manifestations of vitamin A deficiency but apparently do not commonly recognize them. It has been suggested that the cutaneous lesions are among the earliest if not the earliest clinical manifestation of deficiency of vitamin A. There have been numerous reports of the appearance of such lesions, but most of them have been published from observations made in the Orient or in Africa.

In the past year Youmans and Corlette<sup>112</sup> have recorded observations on 6 patients with cutaneous lesions which were considered to be due to vitamin A deficiency. They observed two types of changes—the first consisting of a gooseflesh or horny type of eruption, similar grossly and histologically to the type reported by Frazier and Hu,<sup>113</sup> and the second a type of lesion which resembled in many but not in all respects the acne pustule, with the exception that pustulation was uncommon. Youmans and Corlette, furthermore, emphasized an important point in diagnosis and therapy, namely, that improvement in the cutaneous lesions is seldom noted in less than four weeks and that in many instances twelve to fourteen weeks is required before the eruptions disappear. If the response to vitamin A therapy is to be used as a diagnostic procedure, it is important to remember that the response is slow, depending as it does on anatomic repair, in contrast to the relief of the night blindness of vitamin A deficiency, in which the response to therapy depends on physiologic changes only and therefore occurs in a matter of hours or a few days.

Keil<sup>114</sup> has also published studies on the cutaneous follicular lesions of vitamin A deficiency and has attempted to establish criteria for distinguishing them from the cutaneous lesions of vitamin C deficiency.

In a review of the influence of vitamin therapy on lesions of the skin Stokes, Beerman and Ingraham<sup>115</sup> have come to the conclusion that high vitamin therapy, as far as it concerns cutaneous inflammatory disease, has a not too highly specific but rather a shotgun quality, concerned mainly with the effect of vitamins on the general constitution and nutrition of patients. They have pointed out that the two nearest

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112 Youmans, J. B., and Corlette, M. B. Specific Dermatoses Due to Vitamin A Deficiency, *Am J M Sc* **195** 644-650 (May) 1938.

113 Frazier, C. N., and Hu, C. K. Cutaneous Lesions Associated with Deficiency of Vitamin A in Man, *Arch Int Med* **48** 507-514 (Sept) 1931.

114 Keil, H. The Follicular Lesions of Vitamine A and C Deficiencies. A Critical Survey, *Am J Digest Dis* **5** 40-48 (March) 1938.

115 Stokes, J. H., Beerman, N., and Ingraham, N. R., Jr. Carbohydrate and Water Metabolism and the Vitamins in Skin Inflammation (Dermatitis), *Am J M Sc* **195** 562-574 (April) 1938.

approaches to a specific use for vitamin therapy are found for vitamin A in keratodermic disturbances and their associated pyogenic infections and in senile vaginitis and pruritis vulvae

Clausen<sup>116</sup> has presented an excellent review of the pharmacology and therapeutics of vitamin A in a recent article in *The Journal of the American Medical Association*. Some of his conclusions are worthy of repetition here because they summarize information gathered over a period of recent years which should be of considerable interest to clinicians. Clausen has pointed out that the absorption of vitamin A appears to be accomplished by means of a mechanism which includes linkage of the vitamin with fatty acids, probably in the intestinal wall. This normal process is interfered with when bile is excluded from the intestine during infections and in patients with steatorrhea. Nothing is known of the degree of destruction of vitamin A in the gastrointestinal tract. Evidence that antagonism exists between the action of thyroxine and that of vitamin A is suggested by the following observation. In experimental animals the loss of weight due to daily ingestion of thyroxin could be prevented by the administration of vitamin A. Improvement of patients with various types of disease of the thyroid following the use of vitamin A in large amounts has been reported.

Clausen<sup>116</sup> has found that the majority of investigators fail to obtain evidence that a deficiency of vitamin A alone will cause stone in the urinary tract. The influence of moderate vitamin A deficiency on the reproductive organs of the male is unknown, while for the female the characteristic change is in the vaginal mucous membrane, which becomes permanently cornified. There also may be an effect on or through the ovary, but the effect on the hypophysis is unknown.

Anemia is not a regular symptom of vitamin A deficiency, and the use of vitamin A for the treatment of anemia does not rest on a secure foundation. In fact, Clausen<sup>116</sup> concludes that no striking effect of vitamin A deficiency on the cellular elements of the blood has been discovered.

Vitamin A has been sold for some years as the "anti-infectious vitamin," without much justification. On this point Clausen has said

The evidence reviewed indicates that severe deficiency of vitamin A lowers resistance to infection in man and that the administration of vitamin A during the course of an infection probably has no beneficial effect on the outcome unless severe deficiency is present. There is evidence that moderate deficiency of vitamin A may also increase the duration or severity of respiratory infections in man, that an adequate intake of vitamin A may lessen the severity and duration of infection in persons moderately deficient. It is also evident that many other factors

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116 Clausen, S. W. The Pharmacology and Therapeutics of Vitamin A. *J. A. M. A.* **111** 144-154 (July 9) 1938.

are of equal or greater influence on infection, and no justification exists for calling vitamin A "the anti-infective vitamin"

*Effect of Vitamin A on Nutritional Well-Being*—While vitamin A in small quantities is indispensable for normal health, there has been much discussion of the possible effect of optimal doses on healthy animals and on man. Sherman and Campbell<sup>117</sup> in their studies of rats have found that the three factors which were increased in greatest ratio when an already adequate diet was modified to constitute a nutritionally better diet were calcium, vitamin A and riboflavin. On the other hand, Lewis and Barenberg<sup>118</sup> sought information on the margin of safety with respect to the vitamin A content of the average diet of infants. To 51 infants they gave a diet which contained approximately one-fourth the vitamin A content of the average diet, and to 53 infants they gave a diet which contained from four to eight times the number of vitamin A units contained in the average diet (the average diet contained 2,100 to 4,700 U S P units of vitamin A, depending on the age of the infant). After an average period of six to eight months a comparison of the nutritional status and incidence of infection in the two groups was made. The results showed that there was no difference between the two groups in either of these respects, which led the authors to conclude that the average diet of infants contains at least four times as many units as the minimum requirement, as judged by the nutritional state of infants and by their reactions to infection.

*Diagnostic Procedures for Vitamin A Deficiency*—Eyes. Since the earliest clinical manifestations of vitamin A deficiency have to do with the eyes, it is natural that efforts to make a diagnosis of early vitamin A deficiency would rest in part on efforts to measure by laboratory or other procedures those changes in the eyes which are characteristic of vitamin A deficiency. In general, such methods fall into two groups: the first, examination of epithelial cells scraped from the bulbar conjunctiva and, the other, estimation of the ability of the eyes to adapt themselves to darkness. The former method of examining smears for keratinized cells is believed by Youmans and his associates<sup>119</sup> to be inadequate.

The latter method of examination is based on the well established fact that moderately severe vitamin deficiency is accompanied by an

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117 Sherman, H. C., and Campbell, H. L. Nutritional Well-Being and Length of Life as Influenced by Different Enrichments of an Already Adequate Diet. *J. Nutrition* **14** 609-620 (Dec.) 1937.

118 Lewis, J. M., and Barenberg, L. H. The Relationship of Vitamin A to the Health of Infants. *J. A. M. A.* **110** 1338-1341 (April 23) 1938.

119 Youmans, J. B., Corlette, M. B., Corlette, M. G., and Frank, H. Inadequacy of Conjunctival Smears in Diagnosis of Slight Vitamin A Deficiency in Adults. *J. Lab. & Clin. Med.* **23** 663-670 (April) 1938.

abnormality of the dark adaptation reaction. Measurements of alterations of dark adaptation have been made in large part in this country by the biophotometric method popularized by Jeans and Zentmire.<sup>120</sup> There has been much discussion of the value of this method as a diagnostic procedure, and in my opinion there is still sufficient evidence to suggest that the test cannot be considered a satisfactory or a reliable method for detecting mild forms of vitamin A deficiency. The extensive studies of Jeghers,<sup>121</sup> noted last year, indicated that the method was of value, and more recently Corlette, Youmans, Frank and Corlette<sup>122</sup> have reported that they have found the method satisfactory for the making of photometric studies of adults. They have proposed an initial recovery reading of 0.70 milli-foot-candle as a tentative value for the normal limit of dark adaptation. Using this criterion they found that 50 per cent of a group of ambulatory adult outpatients had poor dark adaptation, indicating mild vitamin A deficiency. The great majority of these patients improved after treatment with vitamin A.

On the other hand, Snelling,<sup>123</sup> Palmer and Blumberg<sup>124</sup> and more recently Palmer<sup>125</sup> have collected information which they feel casts doubt on the value of the biophotometric test as a means of measuring the vitamin A status of patients. The principal criticisms of the method noted by these workers were that the results are variable and have little consistency for children (Snelling<sup>123</sup>), that considerable improvement in readings, apparently due to the learning factor, resulted from repeated testing of the same children (Palmer and Blumberg<sup>124</sup>) and that in one study the results obtained showed no significant difference in the improvement in biophotometric measurements in a group of children whose diet was supplemented by 18,000 U. S. P. units of vitamin A and a control group whose diet was not supplemented with vitamin A.

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120 Jeans, P. C. and Zentmire, Z. A Clinical Method for Determining Moderate Degrees of Vitamin A Deficiency, *J. A. M. A.* **102** 892-895 (March 24) 1934. Jeans, P. C., Blanchard, E., and Zentmire, Z. Dark Adaptation and Vitamin A, *ibid.* **108** 451-456 (Feb. 6) 1937.

121 Jeghers, H. Night Blindness as a Criterion of Vitamin A Deficiency, *Ann. Int. Med.* **10** 1304-1334 (March) 1937.

122 Corlette, M. B., Youmans, J. B., Frank, H., and Corlette, M. G. Photometric Studies of Visual Adaptation in Relation to Mild Vitamin A Deficiency in Adults, *Am. J. M. Sc.* **195** 54-65 (Jan.) 1938.

123 Snelling, C. E. The Biophotometer as a Test for Vitamin A Deficiency, *J. Pediat.* **13** 506-609 (Oct.) 1938.

124 Palmer, C. E., and Blumberg, H. The Use of a Dark Adaptation Technique (Biophotometer) in the Measurement of Vitamin A Deficiency in Children, *Pub. Health Rep.* **52** 1403-1419 (Oct. 8) 1937.

125 Palmer, C. E. The Dark Adaptation Test for Vitamin A Deficiency, *Am. J. Pub. Health* **28** 309-315 (March) 1938.

(Palmer <sup>125</sup>) Furthermore, Booher and Williams,<sup>126</sup> as a result of their quantitative studies of the problem, have concluded that, "provided the worker is equipped with suitable means for frequent calibration of the intensity of light emanating from the illuminated central dot of the test screen and from the large diffusing plate used for light adaptation the biophotometer *may* be adequate for detecting *marked* dysadaptation in adults" <sup>127</sup>

The whole situation has been well summarized by Palmer <sup>125</sup> who thinks that theoretically it is probable that it should be possible to measure quantitatively the vitamin A nutritional status by means of the dark adaptation tests but that as yet the method is not practicable nor satisfactory <sup>1-71</sup>

While the value of the biophotometric test as a measure of vitamin A deficiency is still on trial, the fact that disturbances in dark adaptation may occur in vitamin A deficiency has received practical application in the prevention of night blindness among those who drive automobiles at night and, according to a recent report by Wise and Shettler <sup>128</sup> among color matchers in an industrial organization. These observers have found that by giving three capsules of carotene in oil daily to color-matching inspectors, the efficiency of these workers was improved by 75 per cent and there was a decrease in incidence of headaches and of burning and smarting of the eyes

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126 Booher, L. E., and Williams, D. E. A Study of the Biophotometer as a Means of Measuring the Vitamin A Status of Human Adults, *J. Nutrition* **16** 343-354 (Oct.) 1938

127 The italics have been inserted by me

127a Additional evidence suggesting that measurements of dark adaptation theoretically and practically should be of value in determining the nutritional status of vitamin A of an individual has been presented by Hecht (Hecht, S. Dark Adaptation and the Diagnosis of Avitaminosis A. *Nutrition: The Newer Diagnostic Methods*, Proceedings of the Round Table on Nutrition and Public Health, New York, Milbank Memorial Fund, 1938, p. 32). His studies indicate that the biophotometric test as it ordinarily is performed may not be an accurate measure of dark adaptation because of certain technical defects in the method. He is of the opinion that factors such as the intensity and duration of the preadaptation light, and the area, the retinal location, the color and the duration of the measuring light must be specified for the test to be an adequate one.

An instrument which he and his associates have devised appears to overcome some of the previously stated objections to this test and to satisfy the requirements that have been noted. The results show clearly that cone function is affected by changes in the status of vitamin A just as rod function is affected by them. With this instrument Hecht is able to show an almost immediate rise (within twenty-four hours) in the intensity level of the dark adaptation of healthy persons deprived of vitamin A. In other words, this method seems to be a very sensitive one, and if the findings are verified it may prove to be of great value in the diagnosis of early vitamin A deficiency.

128 Wise and Shettler, cited, Carotene-in-Oil to Ease Eyestrain, *Science News, Science (supp.)* **87** 11-12 (June 10) 1938

Studies of the content of carotene and vitamin A in the blood plasma are gradually adding information not only of physiologic but probably also of diagnostic value. Methods of determining the quantity of vitamin A in plasma are not as satisfactory as are methods of determining the content of vitamin C. In a recent critical analysis of methods of assay of vitamin A Munsell<sup>129</sup> pointed out that the blue color reaction with antimony trichloride is no longer considered to have possibilities as the basis of a specific and dependable quantitative method, although it may still be used routinely for certain purposes of control. She is of the opinion that the spectiographic method of analysis holds promise of eventually becoming an accepted technic for quantitative work, although it is now largely in the investigative stage.

A combination of physiologic and chemical methods of assay of vitamin A has been reported by Dann and Evelyn,<sup>130</sup> who have used a photoelectric colorimeter to measure the blue of the antimony trichloride reaction. They believe that the method will be of value because it combines accuracy with convenience and economy and is entirely objective. The method has apparently been used with success by May<sup>131</sup> in determining the vitamin A content of serum.

In recent studies made by Clausen and McCoord<sup>132</sup> the vitamin A content of the blood plasma (or serum) was estimated by the Price-Carr antimony trichloride reaction. They found the mean values in 119 observations on persons without infections and over 2 years of age to be 20.2 U. S. P. units for each hundred cubic centimeters of plasma, with a standard deviation of 10 units. They observed also that infections cause a prompt and considerable fall in the concentration of carotene, xanthophyll and vitamin A in the plasma, owing in part to low intake during infection and in part to fever. A few days after the temperature becomes normal, the vitamin A content of the plasma may rise considerably above normal. They noted also that in Bright's disease the level of plasma may be greatly elevated, probably because the liver fails to store the vitamin. In hypothyroidism, on the other hand, the vitamin A content of the plasma may be low, and successful treatment with thyroid is said to correct the anomaly.

Van Veen and his associates<sup>133</sup> studied the vitamin A content of the blood serum of native prisoners in Batavia who were on a diet

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129 Munsell, H. E. Vitamin A. Methods of Assay and Sources in Foods, *J. A. M. A.* **111** 245-252 (July 16) 1938.

130 Dann, W. J., and Evelyn, K. A. The Determination of Vitamin A with the Photoelectric Colorimeter, *J. Biochem.* **32** 1008-1017 (June) 1938.

131 May, C., cited by Dann and Evelyn<sup>130</sup>.

132 Clausen, S. W., and McCord, A. B. The Carotenoids and Vitamin A of the Blood, *J. Pediat.* **13** 635-650 (Nov.) 1938.

133 van Veen, A. G., Lanzing, J. C., and Agoes, M. Providing Prisoners with Vitamin A, *Geneesk. tijdschr. v. Nederl.-Indie* **77** 3024-3039 (Nov. 30) 1937.

practically free from vitamin A. Nevertheless, the average content of vitamin A in the serum did not differ greatly from that of persons in Europe and other persons in Batavia because the diet of the Batavian native is high in carotenoid pigments. In other natives of Batavia namely, in children suffering from xerophthalmia, de Haas and Meulemans<sup>134</sup> found as a rule that the serum contained no vitamin A, occasionally a trace was present. They observed that if the cornea was not perforated, even though temporarily there was no vitamin A in the blood, treatment with a preparation of vitamin A would relieve the disease of the eye.

*Therapy with Vitamin A*—There has been no significant change in the treatment of vitamin A deficiency. Concentrates of the vitamin are available principally in the form of concentrated fish liver oils. Carotene is also available as a therapeutic agent. Effective therapeutic doses are in the neighborhood of 10,000 to 70,000 U. S. P. units daily. As yet a satisfactory preparation of the vitamin which may be conveniently administered parenterally is not available. Carotene, cod liver oil and concentrates of vitamin A have been given intramuscularly, but their widespread clinical use is not practical. Reports such as that of Leak<sup>135</sup> on the effect of parenteral administration of vitamin A are based on the use of the vitamin in a form specially prepared for this method of administration.

There is little to fear in the way of toxic effect from therapeutic use of vitamin A. Further substantiation of this fact is provided in the work of Vedder and Rosenberg,<sup>136</sup> who used a preparation of jewfish liver oil on rats and found that if the vitamin is ever toxic it is in doses in excess of 100,000 U. S. P. units daily for 50 Gm rats. Similarly, the fear that cod liver oil in average therapeutic doses is toxic is denied by the observation of Burack and Zimmerman,<sup>137</sup> who found that in ordinary therapeutic doses this substance is not injurious.

#### THE VITAMIN B COMPLEX

While the individual components of the vitamin B complex frequently are considered as one group, they differ widely chemically and

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134 de Haas, J. H., and Meulemans, O. Vitamin A and Carotinoids in Blood Deficiencies in Children Suffering from Xerophthalmia, *Lancet* **1** 1110-1111 (May 14) 1938.

135 Leak, W. N. Clinical Observations on the Effect of the Parenteral Administration of Vitamins A and D, *Lancet* **1** 599-603 (March 12) 1938.

136 Vedder, E. B., and Rosenberg, C. Concerning the Toxicity of Vitamin A, *J. Nutrition* **16** 57-68 (July) 1938.

137 Burack, E., and Zimmerman, H. M. Studies on the Alleged Toxic Action of Cod Liver Oil, *J. Nutrition* **14** 535-551 (Dec.) 1937.

physiologically and in their clinical behavior. In the past year two substances which have been obtained in crystalline form have been identified definitely as components of the complex, these are nicotinic acid and vitamin B<sub>6</sub>.

The components originally were separated into groups because of their ability to promote growth of rats or to cure or prevent polyneuritis or beriberi. Subsequently it was shown that the substance or substances which were necessary for growth were thermostable, and to them was given the name vitamin B<sub>2</sub> or G. The antineuritic element was shown to be thermolabile and is now known as vitamin B<sub>1</sub>, thiamin or aneurin. More recent studies have demonstrated other thermolabile factors. Williams and Spies<sup>138</sup> have listed the thermolabile factors as follows:

- 1 Vitamin B<sub>1</sub>, thiamin or aneurin
- 2 Vitamin B<sub>1</sub>, necessary in addition to 1 for the weight maintenance of pigeons
- 3 Vitamin B<sub>1</sub>, regarded as necessary for growth of rats and to protect them against a paralysis
- 4 W factor, the alcohol ether precipitate from liver extract. Protein in nature
- 5 Antigizzard erosion factor, perhaps identical with or related to B<sub>3</sub>

Even more confusing to chemists and clinicians than the thermolabile components of the vitamin B complex are the members of the thermostable group. As Williams and Spies<sup>138</sup> have emphasized, the diversity of results reported by various investigators who have tried to classify these components appears to be due to dependence on a variety of raw materials and on the use of various fractionation methods as well as on differences in the species of animals chosen for test purposes. These authors have listed the components of the thermostable group as follows:

#### Adsorbed

- 1 Riboflavin, rat growth promoting, cataract preventing, turkey dermatitis preventing
- 2 Nicotinic acid, black tongue and pellagra curative (perhaps not the sole pellagra vitamin)
- 3 B<sub>6</sub>, ill defined thermostable pigeon weight factor
- 4 B<sub>6</sub>, rat growth promoting, anti-acrodynia factor isolated but not identified, also called factor 1

#### Unadsorbed (Filtrate Factors or Factor 2)

- 1 Chick dermatitis factor
- 2 Gray hair preventing factor

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<sup>138</sup> Williams, R. R., and Spies, T. D. Vitamin B<sub>1</sub> and Its Use in Medicine, New York, The Macmillan Company, 1938.



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## Unclassified Factors Possibly Associated with the B Complex

- 1 Extrinsic factor
- 2 Anti-egg white injury factor
- 3 Antianemic factor
- 4 Choline factor

Of these factors in the B complex, thiamin and nicotinic acid have been found to be of great therapeutic importance in man, while riboflavin and vitamin B<sub>6</sub>, which have been identified and obtained in crystalline form, have not been definitely identified as agents of therapeutic importance. The other possible components noted in this list are as yet not identified, and there is considerable discussion as to their importance in the nutrition of man and, in fact, as to their existence.

*Vitamin B<sub>1</sub> (Thiamin Chloride)*—Chemistry and Physiology. The chemistry of thiamin is well known, and details of its properties may be found in the book by Williams and Spies<sup>138</sup> or in an article by Williams.<sup>139</sup> Apparently the substance has an important role in the enzyme system, resulting in the oxidation of carbohydrates and particularly of pyruvic and lactic acid, and it participates in the function of several other enzyme systems as well. It is likely that the vitamin or a molecule of which the vitamin is a part is coupled with a protein carrier and that either the combination exhibits enzymatic activity or in certain instances the vitamin may be a member of a system which is necessary for the activation of an important enzyme. Indeed, as Williams<sup>140</sup> has pointed out, thiamin is the most conspicuous example of those vitamins which possess a universal or nearly universal function in living cells.

A further suggestion that thiamin may play a role in fat metabolism has been given by Gavin and McHenry,<sup>141</sup> who found that in rats the substance causes an accumulation of dietary or synthesized fat in the liver. On the contrary, vitamin B<sub>6</sub> promotes storage of such fat in the fat depots.

**Requirement of Vitamin B<sub>1</sub>**. Little information has been added to estimates of the requirement of vitamin B<sub>1</sub> noted in the review of last year.<sup>142</sup> A daily intake of 1 or 2 mg. in food by adults apparently satisfies the requirement of man for this substance. Cowgill<sup>143</sup> has

139 Williams, R. R. The Chemistry of Thiamin (Vitamin B<sub>1</sub>), *J. A. M. A.* **110** 727-732 (March 5) 1938.

140 Williams, R. R. The Chemistry and Biological Significance of Thiamin, *Science* **87** 559-563 (June 24) 1938.

141 Gavin, E. G., and McHenry, E. W. The Relation of the Vitamin B Complex to Fat Metabolism, *J. Nutrition (supp.)* **15** 10 (June) 1938.

142 Wilder, R. M., and Wilbur, D. L. Diseases of Metabolism and Nutrition, *Arch. Int. Med.* **61** 297-365 (Feb.) 1938.

143 Cowgill, G. R. Human Requirements for Vitamin B<sub>1</sub>, *J. A. M. A.* **111** 1009-1016 (Sept. 10) 1938.

pointed out that the requirement for vitamin B<sub>1</sub> may be influenced by such clinical factors as the level of energy metabolism, which is affected principally by fever and hyperthyroidism, and by the loss of the vitamin through excretory channels, such as occurs with diarrhea and diuresis. Estimations of the vitamin requirement of an individual have been accomplished in the past by such means as Cowgill's formula, the calculation being based on the weight of the individual and on the vitamin-calory ratio of his diet. Cowgill<sup>143</sup> further has pointed out that estimates derived from his formula pertain to the minimum or beriberi-preventing level and that the optimal level is undoubtedly much higher. Williams and Spies,<sup>138</sup> after a careful analysis of the situation, feel that a "thiamin-non-fat-calorie ratio" is the best tentative index of adequacy for protection of the average individual that can be offered at present.

Knott and Schlutz<sup>144</sup> have reported that the requirement of infants for vitamin B<sub>1</sub> is higher for each unit of body weight than that of older children. The determinations in their study were made by retention studies, and the authors noted that in the case of infants the vitamin is almost completely absorbed, as contrasted with the findings for older children, who excrete considerable quantities in the feces.

**Adequacy of Vitamin B<sub>1</sub> in the Average Diet.** A problem of great interest and importance is that of the adequacy of the vitamin B<sub>1</sub> content of the average diet. In the work of Baker, Wright and Drummond,<sup>145</sup> noted in the review of last year, evidence was presented to show that the best fed members of the population in Great Britain today, while receiving twice as much vitamin B<sub>1</sub> as is received by persons with a low income, consume less vitamin B<sub>1</sub> than did the parish poor of the eighteenth and early nineteenth centuries. More recently Jolliffe<sup>146</sup> has published studies of the vitamin B<sub>1</sub> content of the average American diet. He has noted that, as in the case of the British, Americans in 1840 consumed about three times the amount of vitamin B<sub>1</sub> that is obtained by the average American today. Jolliffe is of the opinion that the margin of safety as regards the vitamin B<sub>1</sub> content of the American diet varies from 20 to 80 per cent and that a large proportion of the population, particularly those spending less than \$2 per week per capita for food, subsist on diets of borderline adequacy of vitamin B<sub>1</sub>. The consequence is, as Strauss<sup>147</sup> has stated, that beriberi is really endemic in this country.

144 Knott, E, and Schlutz, F W. The Vitamin B Requirement of Infants, *J Nutrition* (supp.) **15** 16-17 (June) 1938.

145 Baker, A Z, Wright, N D, and Drummond, J C, cited by Jolliffe<sup>146</sup>

146 Jolliffe, N. A Clinical Evaluation of the Adequacy of Vitamin B<sub>1</sub> in the American Diet, *Internat Clin* **4** 46-66 (Dec) 1938.

147 Strauss, M B. The Therapeutic Use of Vitamin B<sub>1</sub> in the Polyneuritis and Cardiovascular Conditions, *J A M A* **110** 953-956 (March 26) 1938.

**Role of Vitamin B in Resistance** Studies of deficiency diseases produced in animals by inadequate feedings of vitamins have revealed that infections of various types are commonly prominent features of the resulting deficiency states. For a time vitamin A was presumed to be the "anti-infective vitamin," but more recently vitamin C has taken its place, because of its apparently important role in the processes of immunity. Not much stress has been placed on a possible role for vitamin B in resistance, but within the past year Perla<sup>148</sup> has reviewed much of the evidence that is available on this subject. He has considered the components of the vitamin B complex as a group, with the exception that in some of the reports that he has reviewed the results were considered in terms of vitamin B<sub>1</sub> alone. He has noted that scattered evidence reported in the literature indicates an increase in frequency of spontaneous infections in animals and in man fed diets deficient in vitamin B. Apparently the role of vitamin B in natural resistance is indirect and is secondary to its importance in cellular metabolism and in the processes of oxidation. A definition of the relative importance of the various components of this vitamin in resistance is not possible at present.

**Methods of Determining Vitamin B<sub>1</sub>** During the past year some advance has been made in the determination of vitamin B<sub>1</sub> and in assays of the content of the vitamin in various body fluids and excretions. Previously most studies involving assay of vitamin B<sub>1</sub> have been accomplished by means of biologic methods, but in recent years chemical methods have been developed. An excellent summary of these biologic and chemical methods of assay has been given by Munsell<sup>149</sup>.

The most widely studied method of chemical assay of thiamin is the thiochrome method. By using this method improved by details in technic, Ritsert<sup>150</sup> expressed the opinion that he could determine amounts of thiamin as small as approximately 1 international unit per hundred cubic centimeters of urine. He suggested that 30 to 150 international units is excreted in the urine daily. This contrasts with the findings of Harris and Leong<sup>151</sup> who used the bradycardia method, which is a biologic method. They found that the daily output is from 12 to 35 international units.

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148 Perla, D. Role of Vitamin B in Resistance, *Arch Path* **25** 539-568 (April), 694-729 (May) 1938.

149 Munsell, H. E. Vitamin B<sub>1</sub>, Methods of Assay and Food Sources, *J A M A* **111** 927-934 (Sept 3) 1938.

150 Ritsert, K. Zur Aneurinbestimmung im Harn nach der Jansenschen Thiochrommethode, *Deutsche med Wchnschr* **64** 481-484 (April 1) 1938.

151 Harris, L. J., and Leong, P. C. Vitamins in Human Nutrition. The Excretion of Vitamin B<sub>1</sub> in Human Urine and Its Dependence on the Dietary Intake, *Lancet* **1** 886-894 (April 18) 1936.

In a more recent study Rowlands and Wilkinson,<sup>152</sup> using the biologic method of Schopfer's phycomyces test, have reported their studies of the clinical significance and estimation of vitamin B<sub>1</sub> in the blood. They are of the opinion that the method can be developed as a reasonable test for vitamin B<sub>1</sub> nutrition and that it appears to be the best method at present available for dealing with the small quantities of vitamin B<sub>1</sub> in the blood. The test is too laborious and exacting in technic to serve as an ordinary routine laboratory method. They have placed the range for the vitamin B<sub>1</sub> content of the blood of 8 normal subjects at 6.5 to 16.5 micrograms per hundred cubic centimeters. This compares favorably with the figures of Meiklejohn,<sup>153</sup> previously reported. Gross deficiencies in the vitamin B<sub>1</sub> content of the blood were present in cases of alcoholic neuritis, nutritional neuritis, scurvy and malnutrition, and partial deficiency was present in simple anemia due to achlorhydria. Sinclair<sup>154</sup> has objected to the results reported by Rowlands and Wilkinson,<sup>152</sup> because he believes that they are statistically worthless and that the method of analysis which was used does not give quantitative estimates of the vitamin B<sub>1</sub> content of the blood.

As Williams and Spies<sup>138</sup> have stated, "Chemical methods of assay are promising but as yet insufficiently developed for the study of foods, those involving growth of microorganisms require more vigorous proof of specificity before they can be trusted for general purposes."

**The Effect of Vitamin B<sub>1</sub> Deficiency, Diagnosis and Treatment**  
**1 Nervous system** It is generally agreed that the peripheral neuritis of beriberi is caused by deficiency of this vitamin. The evidence for this has been tabulated by Williams and Spies<sup>138</sup> and by Jolliffe.<sup>146</sup> The frequency with which the symptoms of polyneuritis of beriberi occur in the general population is unknown. Jolliffe and Frank<sup>155</sup> found that 61.6 per cent of 1,000 men admitted consecutively to the ward for alcoholic addicts at Bellevue Hospital in the fall of 1935 had polyneuritis. The condition is observed not uncommonly in women during gestation and in persons with chronic gastrointestinal disorders, diabetes mellitus and hyperthyroidism.

Shattuck<sup>156</sup> has recently reviewed reports of cases of Landry's paralysis or syndrome and has reported that the features of the original cases reported by Landry are consistent with a diagnosis of beriberi.

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152 Rowlands, E. N., and Wilkinson, J. F. The Clinical Significance and Estimation of Blood Vitamin B<sub>1</sub>, *Brit. M. J.* **2** 878-883 (Oct. 29) 1938.

153 Meiklejohn, A. P. The Estimation of Vitamin B<sub>1</sub> in Blood by a Modification of Schopfer's Test, *Biochem. J.* **31** 1441-1451 (Sept.) 1937.

154 Sinclair, H. M. Estimation of Blood Vitamin B<sub>1</sub>, *Brit. M. J.* **2** 1060 (Nov. 19) 1938.

155 Jolliffe, N., and Frank, P., cited by Jolliffe.<sup>146</sup>

156 Shattuck, G. C. "Landry's Paralysis" in Relation to Vitamin B<sub>1</sub> Deficiency, *Internat. Clin.* **3** 24-29 (Sept.) 1938.

He feels that a noteworthy proportion of conditions so diagnosed are due to deficiency of vitamin B<sub>1</sub>.

The early diagnosis of the polyneuritis of beriberi is of great importance. Goodhart and Jolliffe<sup>157</sup> have used the following criteria to designate mild involvement: "The signs must be limited to the lower extremities with the knee jerks preserved and with no obvious muscle atrophy or foot drop, the patient must show absent ankle jerks plus some demonstrable sensory changes such as muscle tenderness, skin hyperesthesia in a peripheral nerve distribution and impairment of vibratory or position sense." Vedder<sup>158</sup> has described the following points as of early diagnostic value: 1. Slight pressure over the muscles of the calf causes pain. 2. Patients with beriberi often have areas of anesthesia over the anterior surface of the tibia. 3. Any modification of the patellar reflexes is suspicious. 4. If a patient with beriberi squats on his heels after the Oriental manner of sitting, he may experience pain and an inability to rise without using his hands. The excellent description by Strauss<sup>147</sup> of the early symptoms of polyneuritis of beriberi was noted in last year's review.

The treatment of polyneuritis of beriberi has become highly successful since the introduction of concentrated and crystalline forms of the vitamin. The principal problem in this respect at present is to determine the optimal amount of vitamin B<sub>1</sub> which should be given. As a result of their studies of 17 alcoholic addicts having uncomplicated polyneuritis, Goodhart and Jolliffe<sup>157</sup> feel that improvement in the objective signs of the polyneuritis varies directly with the vitamin B<sub>1</sub> intake up to a point of optimal dosage, which though not yet determined, is definitely more than four times the predicted maintenance dose. Williams and Spies<sup>138</sup> advocated for the adult with polyneuritis a well rounded diet of 4,500 calories, including food of high vitamin B<sub>1</sub> value, supplemented whenever possible by one or several of the following items: dried brewer's yeast (6 ounces [170 Gm]), wheat germ (6 ounces daily) or crystalline vitamin B<sub>1</sub> (10 mg twice daily). The crystalline vitamin B<sub>1</sub> may be given parenterally if there is interference with gastrointestinal function. Stern<sup>159</sup> has advocated giving thiamin intrathecally for a variety of neurologic disorders, but there seems to be little advantage in giving it in this way as compared to its administration by the intramuscular or intravenous route.

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157 Goodhart, R., and Jolliffe, N. Effects of Vitamin B (B<sub>1</sub>) Therapy on the Polyneuritis of Alcohol Addicts, *J A M A* **110** 414-419 (Feb 5) 1938

158 Vedder, E. B. Beriberi and Epidemic Dropsy, in Tice, F. Practice of Medicine, Hagerstown, Md, W. F. Prior Company, Inc., 1936, vol. 4

159 Stern, E. L. Intraspinal (Subarachnoid) Injection of Vitamin B<sub>1</sub> for Relief of Intractable Pain, and for Inflammatory and Degenerative Diseases of Central Nervous System. Preliminary Report, *Am J Surg* **39** 495-511 (March) 1938

An observation indicating that the acute neuritis of leprosy may be due to vitamin B<sub>1</sub> deficiency was given in the report by Badger and Patrick<sup>160</sup> They had under their care patients with leprosy who had extremely severe pain and who obtained relief from pain in some cases in as short a time as twenty-four hours Apparently the results were obtained when the preparation of vitamin B<sub>1</sub> was given parenterally but not when it or yeast was given by mouth

2 Cardiovascular effects During the past year little of clinical interest has been added to the knowledge of the cardiovascular symptoms and signs of beriberi noted in the review of last year

3 Anemia There has been much discussion of the relation of components of the vitamin B complex and anemia The original theory that the extrinsic factor of pernicious anemia might be vitamin B<sub>2</sub> (G) was subsequently shown to be erroneous There has been little evidence to suggest that anemia which may accompany beriberi is due to deficiency of vitamin B<sub>1</sub> Recently Bianco and Jolliffe<sup>161</sup> reported that in 159 of 189 cases of alcohol addiction that condition was "complicated" by one or more of the following disorders: polyneuritis, pellagra, alcoholic stomatitis, encephalopathy and cirrhosis Macrocytosis of the erythrocytes was noted in 61 per cent of the cases in which there were complications There was no correlation between macrocytosis and achlorhydria, severity of hepatic damage or presence of an enlarged liver These investigators concluded, therefore, that the anemia was not a manifestation of inability on the part of the liver to store a hemopoietic principle but of an extrinsic deficiency of some hemopoietic substance required to maintain normocytosis

4 Gastrointestinal tract The effects of thiamin deficiency on the gastrointestinal tract are still the subject of debate As Strauss<sup>147</sup> has recently pointed out, there is considerable evidence to support the contention that changes in the gastrointestinal tract, such as anorexia, glossitis, achlorhydria and diarrhea, and changes in the blood, such as those indicating anemia which occur in a variety of conditions thought to be due to deficiency of vitamin B<sub>1</sub>, are at least in part if not entirely manifestations of a deficiency of some portion of the vitamin B complex other than thiamin It is of much clinical importance that this matter be settled, which it undoubtedly will be when crystalline preparations of the components of the B complex become available

Cowgill<sup>143</sup> has based many of his studies of the vitamin B<sub>1</sub> requirement of man on the supposition that anorexia is the earliest manifesta-

160 Vitamin B<sub>1</sub> Injections in Acute Neuritis of Lepers, *Science News*, *Science* (supp.) **88** 8 (July 1) 1938

161 Bianco, A., and Jolliffe, N. The Anemia of Alcohol Addicts, *Am J M Sc* **196** 414-420 (Sept) 1938



tion of vitamin B<sub>1</sub> deficiency Schlutz and Knott<sup>162</sup> and others are also of the opinion that the intake of vitamin B<sub>1</sub> is related to the appetite, after observations on the appetite of 54 children carefully observed over a period of thirty-two weeks. After a control period, in which a regular diet containing 260 to 420 international units of vitamin B<sub>1</sub> was given daily, to one group was given stabilized wheat germ and to another crystalline vitamin B<sub>1</sub> as a supplement in amounts of 120 to 200 international units. These supplements produced increases of 17 to 25 per cent in grams of food consumed per child per day. There were no apparent ill effects, growth was not forced, but the supplement did tend to stabilize the appetite. In these studies the stimulation of the appetite seemed to be approximately the same in the group which received wheat germ and the one which received crystalline vitamin B<sub>1</sub>.

The effect of vitamin B<sub>1</sub> on the liver is not certain. The occurrence of cirrhosis in chronic alcoholic addicts with or without accompanying signs of vitamin B<sub>1</sub> deficiency has suggested to some clinicians the possibility that cirrhosis might be due to a deficiency of vitamin B. Patek<sup>163</sup> observed 10 patients with cirrhosis to whom he gave the usual treatment for this disease and in addition supplements high in vitamin B content. He concluded that some of the patients responded more satisfactorily to treatment than do patients with cirrhosis to ordinary forms of therapy.

It has long been known that in many cases diarrhea accompanies vitamin B deficiency, and in such cases there has always been the question as to whether the diarrhea led to the development of the deficiency disease or whether the diarrhea was the result of it or both. Dann and Cowgill<sup>164</sup> have recently reported studies of the effect of artificially induced diarrhea on the absorption of vitamin B<sub>1</sub> from the intestine of the dog. Under the conditions of the experiment they observed a decrease in absorption of an appreciable portion of the ingested vitamin, and in some cases the daily intake of the vitamin by mouth had to be increased as much as 70 per cent above the dose which previously had been adequate to prevent the development of anorexia. Of even more practical clinical value may be the report of Cheney,<sup>165</sup> who found that of 13 patients with diarrhea of the type classified as symptomatic diarrhea or that due to irritability of the

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162 Schlutz, F. W., and Knott, E. M. The Effect of Varied Vitamin B Ingestion upon the Appetite of Children, *J. Nutrition* **15** 411-427 (May) 1938.

163 Patek, A. J., Jr. Treatment of Alcoholic Cirrhosis of the Liver with High Vitamin Therapy, *Proc. Soc. Exper. Biol. & Med.* **37** 329-330 (Nov.) 1937.

164 Dann, M., and Cowgill, G. R. The Influence of Diarrhea on the Vitamin B<sub>1</sub> Requirement, *Arch. Int. Med.* **62** 137-150 (July) 1938.

165 Cheney, G. Vitamin B<sub>1</sub> and Liver Extract in the Treatment of Non-Specific Chronic Diarrhea and Colitis, to be published.

colon, 10 showed beneficial effects after administration of vitamin B<sub>1</sub>. Of interest in this connection is the fact that relatively small doses (in all cases only 1 to 3 mg) were used, that recurrence of diarrhea generally followed cessation of administration of the vitamin and that in some cases it was necessary to give the vitamin parenterally in order to obtain satisfactory results.

*Riboflavin*—During the past year there have been no studies of clinical interest in regard to this substance. Those who may be interested in the nutritional importance of riboflavin are referred to the review of last year and to the articles by Hogan<sup>166</sup> and by Sherman and Lanford<sup>167</sup> in the current series on vitamins in *The Journal of the American Medical Association*. States of deficiency of riboflavin have not been reported in man, and overdoses apparently are not toxic.

*Pellagra-Preventive Factor (Nicotinic Acid?)*—Since the days of Goldberger there has been much speculation as to the chemical nature of the pellagra-preventive or P-P factor. Within the past fifteen months interest in this subject and consequently in the treatment of pellagra has been tremendously stimulated by the observation that nicotinic acid, isolated originally from rice polishings and yeast by Funk in 1911, has a curative effect in cases of pellagra. In fact, the outstanding development in nutrition during the past year has been in relation to the effect of nicotinic acid in pellagra. The importance of this discovery is difficult to estimate when one considers the number of pellagrins in this country and the rapidly curative effect of such an inexpensive substance as nicotinic acid. Nicotinic acid already has been accepted by the Council on Pharmacy and Chemistry for inclusion in New and Nonofficial Remedies for purposes of standardization and clinical experimentation on its use in pellagra. The experimental dose is 0.5 Gm. in five 0.1 Gm. doses daily.

In a recent study Spies, Bean and Stone<sup>168</sup> reported their observations on the effect of nicotinic acid in a series of 73 patients with pellagra. In this group of patients were included those with endemic pellagra as well as those with the disease secondary to other diseases or to chronic alcoholism. They noted that "within seventy-two hours of administration of large amounts of nicotinic acid, sodium nicotinate, nicotinic acid amide or coramine there was fading of the mucous membrane lesions, blanching of the erythema of the cutaneous lesions when present, a tendency toward the return of normal gastro-intestinal func-

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166 Hogan, A. G. Riboflavin. Physiology and Pathology, J. A. M. A. **110** 1188-1193 (April 9) 1938.

167 Sherman, H. C., and Lanford, C. S. Riboflavin. Dietary Sources and Requirements, J. A. M. A. **110** 1278-1280 (April 16) 1938.

168 Spies, T. D., Bean, W. B., and Stone, R. E. The Treatment of Sub-clinical and Classic Pellagra, J. A. M. A. **111** 584-592 (Aug. 13) 1938.

tion [and] remission of mental abnormalities when they were present

" Further observations of note were that there was no special healing effect on the dermatitis in cases in which the continuity of the skin had been broken and in which the lesions were moist and ulcerated or dry and thickened. The peripheral neuritis present in 10 cases was not relieved by nicotinic acid, although the pain and numbness associated with this condition disappeared within forty-eight hours after injection of 50 mg of vitamin B<sub>1</sub> twice a day.

In another article Spies and his associates<sup>169</sup> have discussed in detail the effect of nicotinic acid on the mental symptoms of pellagra. The most common types of psychoses in pellagra are those associated with loss of memory, disorientation, confusion and confabulation. Excitement, mania, depression and delusions may occur. Other less marked symptoms may be those usually classified as neurasthenic. Apparently nicotinic acid in adequate amounts is a specific therapeutic agent for the acute mental symptoms of pellagra, while psychoses in nonpellagious patients failed to respond to the administration of this substance. The "prodromal" or "neurotic" symptoms of pellagra usually disappeared after administration of nicotinic acid.

Manson-Bahr and Ransford<sup>170</sup> have emphasized in particular the importance of the use of nicotinic acid in the treatment of stomatitis, which they feel may be pellagra without cutaneous lesions.

Spies and his associates<sup>168</sup> also have recorded the effect of nicotinic acid in 100 adults without pellagra. They noted that in 50 per cent of the cases a dose of 100 mg on an empty stomach would lead to a cutaneous response consisting of flushing, burning, itching and a sensation of increased local heat in the skin. In occasional subjects there were nausea, vomiting and cramps, but there was no constant deviation in blood pressure or in pulse or respiratory rate.

Is Nicotinic Acid the Only Pellagra-Preventive Factor? The answer to this question is not clearcut as yet, but it probably is to be answered in the negative. Spies and Aring<sup>171</sup> have shown, for example, that the pain and numbness caused by peripheral neuritis of pellagra are not relieved by nicotinic acid, whereas thiamin will promptly relieve them. It has been demonstrated that the healing of well developed cutaneous lesions of pellagra is not apparently stimulated by nicotinic acid. These observations indicate that in the treatment of pellagra a generous diet

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169 Spies, T. D., Aring, C. D., Gilperin, J., and Bean, W. B. The Mental Symptoms of Pellagra: Their Relief with Nicotinic Acid, *Am J M Sc* **196** 461-475 (Oct.) 1938.

170 Manson-Bahr, P., and Ransford, O. N. Stomatitis of Vitamin B<sub>2</sub> Deficiency Treated with Nicotinic Acid, *Lancet* **2** 426-428 (Aug. 20) 1938.

171 Spies, T. D., and Aring, C. D. The Effect of Vitamin B<sub>1</sub> on the Peripheral Neuritis of Pellagra, *J A M A* **110** 1081-1084 (April 2) 1938.

high in its quantity of vitamins and calories should be as much a part of the treatment as is nicotinic acid

Further evidence for the multiple nature of the deficiency has been suggested by the experimental work of Helmer and Fouts,<sup>172</sup> who found that rats fed a diet that causes black tongue, which is equivalent to a pellagra-producing diet in man, supplemented only with nicotinic acid grew less than rats fed supplemented diets

**Diagnosis of Pellagra** The diagnosis of pellagra is made on the basis of clinical findings. The specific nature of the response of pellagra to therapy with nicotinic acid may be of some value. Laboratory tests for the disease have not been developed, although Spies and his associates,<sup>173</sup> in confirming the clinical diagnosis, suggested that the presence of increased porphyrinuria may be used as an early objective test

**Therapeutic Doses of Nicotinic Acid and Its Mode of Action** The minimal therapeutic dose of nicotinic acid has not been determined, but it seems to vary from case to case. Ruffin<sup>174</sup> reported that doses of 70 to 100 mg daily result in prompt recovery and are as effective in the average case of acute pellagra as are doses ten times as large. However, most observers who have studied this problem recommend the use of larger doses

The usual dose of nicotinic acid employed by Spies and his associates<sup>173</sup> was 50 to 100 mg five or six times daily, with variations in the daily dose of 50 mg to 1 Gm. The response of the individual pellagrin may vary considerably, and in some cases it may be necessary to give the substance parenterally

For "monkey pellagra" Harris<sup>175</sup> suggested that the minimum curative dose of nicotinic acid is approximately 2.5 mg daily per kilogram. For the dog Elvehjem and his associates<sup>176</sup> found 0.5 to 1.5 mg per kilogram per day to be a minimum dose

The amount of nicotinic acid which will prevent relapse of pellagra is also unknown, but Schmidt and Sydenstricker<sup>177</sup> reported that 100

172 Helmer, O. M., and Fouts, P. J. Multiple Nature of the Deficiency of Blacktongue-Producing Diets as Shown by Studies on Rats, *J. Nutrition* **16**: 271-277 (Sept.) 1938

173 Spies, T. D., Sasaki, Y., and Cross, E. A Note on the Relationship of Porphyrinuria and Human Pellagra, *South. M. J.* **31**: 483-486 (May) 1938

174 Ruffin, J. M., in discussion on Spies and others<sup>168</sup>

175 Harris, L. J. The Vitamin B<sub>2</sub> Complex. VIII. Further Notes on "Monkey Pellagra" and Its Cure with Nicotinic Acid, *Biochem. J.* **32**: 1479-1481 (Sept.) 1938

176 Elvehjem, C. A., Madden, R. J., Strong, F. M., and Woolley, D. W. Isolation and Identification of the Anti-Blacktongue Factor, *J. Biol. Chem.* **123**: 137-149 (March) 1938

177 Schmidt, H. L., Jr., and Sydenstricker, B. P. Nicotinic Acid in the Prevention of Pellagra, *J. A. M. A.* **110**: 2065-2066 (June 18) 1938

mg orally administered twice weekly was not effective in preventing relapse in patients with chronic pellagra

The mode of action of nicotinic acid is unknown. The observations of numerous workers suggest that lack of this substance leads to cellular alterations in the alimentary tract, skin and other symptoms

*Vitamin B<sub>6</sub>*—Isolation of chemically pure crystals of vitamin B<sub>6</sub> has been reported by Paul Gyorgy<sup>178</sup> and by Lepkovsky<sup>179</sup>. This component of the vitamin B complex is the rat antidermatitic factor, and its relation to human nutrition is unknown

#### VITAMIN C

*Chemistry and Physiology*—The chemistry of vitamin C is well established. In a recent review of the subject, King<sup>180</sup> emphasized the important points for those who are interested in them. A fact of importance to pharmacists and physicians is that although vitamin C is easily oxidized, King<sup>180</sup> stated that the dry crystals of the vitamin are stable on exposure to air and daylight at room temperature through a period of several years

The physiology of vitamin C is of great interest, because of the importance of the vitamin in its most clearly established role of maintaining the physical state of "intercellular material". Because of this function the vitamin is closely related to the metabolism of calcium and to the growth of bones, teeth and other tissues, such as cartilage and white fibrous tissue. While King<sup>181</sup> believes that at present it is impossible to indicate with certainty any specific relation between vitamin C and the enzymes in animal tissues so far as normal physiologic processes are concerned, it is not unlikely that some of the observed effects of vitamin C in activating or inhibiting enzymes will be proved to be physiologically significant. That a close relation may exist between vitamin C and complement has been suggested by the work of Ecker and his associates,<sup>182</sup> who found that the reversible oxidation-reduction behavior of complement, as a single protein substance, is dependent in large part on the ascorbic acid content of the plasma. The normal activity of complement is contingent on its being present in the reduced

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178 Isolation of Chemically Pure Crystals of Vitamin B<sub>6</sub>, *Science News*, *Science* (supp.) **87** 10 (April 29) 1938

179 Lepkovsky, S. Crystalline Factor 1, *Science* **87** 169-170 (Feb 18) 1938

180 King, C. G. The Chemistry of Vitamin C, *J. A. M. A.* **111** 1462-1464 (Oct 15) 1938

181 King, C. G. The Physiology of Vitamin C, *J. A. M. A.* **111** 1099-1101 (Sept 17) 1938

182 Ecker, E. E., Pillemer, L., Wertheimer, D., and Gradis, H. Ascorbic Acid and Complement Function, *J. Immunol.* **34** 19-37 (Jan) 1938

state, and in this connection vitamin C was found to be the reducing agent of major importance in vivo

King<sup>181</sup> has stated that the anemia which accompanies depletion of vitamin C is thought to be due primarily to dysfunction of the tissues which form the red blood cells rather than to excessive destruction of cells or specific failure in synthesis of hemoglobin

Tannhauser and his associates<sup>183</sup> have suggested that ascorbic acid is a powerful activator of serum phosphatase and that the large increase in phosphatase activity of the serum in certain diseases is not due to an actual increase in this enzyme in the circulation but rather to its activation. However, King and Delory<sup>184</sup> were unable to substantiate this finding

*Requirement of vitamin C*—The requirement of man for vitamin C can be stated more accurately than that for any of the other vitamins. Nevertheless the actual requirement can be expressed only in general terms, for it depends on numerous physiologic variables as well as on the method by which the determination is made. The principal methods by which the requirement of vitamin C is determined are the resistance or fragility of blood capillaries, the excretion of ascorbic acid in the urine and the content of ascorbic acid in the blood. After a long discussion of the various phases of this problem Smith<sup>185</sup> has come to the following conclusions

Three levels of requirement may be considered in terms of the minimum quantities of ascorbic acid required (1) to prevent the slightest decrease in capillary resistance or to maintain uniform excretion of the vitamin barely above that on a vitamin C-free diet, (2) to maintain uniform excretion after a depletion period following a preliminary saturation period and (3) to maintain the tissues in a state of saturation as determined by various modifications of the test dose method. These levels of requirement may conveniently be termed the physiologically indispensable, adequate and saturation values respectively

The range for these three levels may be set between the following limits: for infants, from 8 (newborn) to 50 mg daily, for children, from 22 to 100 mg or more, and for adults, from 28 to 100 mg. Values of about 20 mg daily for infants, 40 mg for children and from 50 to 60 mg for adults may be considered as tentative estimates for the middle or barely adequate level of consumption, with but little margin of safety or allowance for individual variation in requirement

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183 Maddock, S., Tannhauser, S. J., Reichel, M., and Gratton, J. New Conception of Serum Phosphatase, Review of Experimental Work, *New England J Med* **218** 166-169 (Jan 27) 1938

184 King, E. J., and Delory, G. E., cited in Serum Phosphatase and Ascorbic Acid, Annotations, *Lancet* **1** 564-565 (March 5) 1938

185 Smith, S. L. Human Requirements of Vitamin C, *J A M A* **111** 1753-1764 (Nov 5) 1938

These figures are in essential agreement with those of Hamil and his associates,<sup>186</sup> who concluded from extensive studies of 427 infants that the minimal protective dose of vitamin C for average healthy, artificially fed infants appears to be 10 mg per day

There has been some discussion as to whether or not saturation with vitamin C is the truly optimal state of ascorbic acid nutrition. This point is of great practical importance, since few persons, except those to whom the vitamin is given in rather large quantities, are actually saturated with vitamin C. Is there any clinical significance attached to the lack of vitamin C saturation? The answer to this question cannot be satisfactorily given at present, but it seems reasonable to agree with Zilva<sup>187</sup> that the wide margin of "unsaturation" of vitamin C which exists in the case of most persons has no obviously detrimental effect on their health. He feels that to apply to this zone of unsaturation such expressions as "hypovitaminosis C," "latent or potential scurvy" or "vitamin C subnutrition" is not justified by the present state of knowledge.

*Vitamin C Content of Foods and Body Fluids*—Chemical methods have rapidly replaced biologic methods of assay of vitamin C, but Bessey<sup>188</sup> has pointed out that while, in general, chemical methods are more rapid and accurate than the latter, they may lack specificity. Even the biologic methods, such as the preventive method, curative method and tooth method, have a degree of uncertainty, because of the unavoidable variation of individual experimental animals and the indefinite nature of the end point.

With regard to determinations by chemical methods, the principal one of which is that with 2, 6-dichlorophenolindophenol, Bessey<sup>188</sup> feels that the errors in determining the vitamin C content of the blood are of about the same order as those for blood sugar tests. Alternative methods based on the reduction of a variety of chemical substances, such as ferricyanide and phosphotungstic acid, have not been widely adopted, because in some cases these substances react too slowly in acid solution and the color changes often vary with time. Bessey feels that it is important to emphasize that titration of blood and many other substances which have an extremely low vitamin C content has a limited accuracy even when done with greatest care.

Foods which are the richest sources of vitamin C are oranges, lemons, grapefruit (raw or canned), tangerines, tomatoes (raw or canned), fresh strawberries, green peppers and raw cabbage. Eggs and seeds are

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186 Hamil, B. M., Reynolds, L., Poole, M. W., and Macy, I. G. Minimal Vitamin C Requirements of Artificially Fed Infants, *Am J Dis Child* **56** 561-583 (Sept.) 1938

187 Zilva, S. Sufficiency of Vitamin C, *Lancet* **2** 1509 (Dec 25) 1937

188 Bessey, O. A. Vitamin C Methods of Assay and Dietary Sources, *J A M A* **111** 1290-1298 (Oct 1) 1938

devoid of the vitamin, while the vitamin C content of ordinary commercial pasteurized milk is small. In fact, the vitamin C content of milk is oxidized fairly rapidly to an inactive oxidized form. Light, oxygen and riboflavin are factors necessary for this inactivation. In half an hour in sunlight on the doorstep the vitamin C content of a bottle of milk may be reduced 50 per cent, according to Hand, Guthrie and Sharp<sup>189</sup>. In the process of cooking and preparing foods the following factors have a particularly "unfavorable" influence on the vitamin C content: contact with copper utensils, access to air, prolonged heating and alkalinity. While by means of modern commercial methods of canning, with careful control, products can be prepared with a minimum loss of vitamin C, there may be great variation in such products, and one cannot be too sure of the constancy of the vitamin C content of canned products unless it is carefully tested.

The excretion of vitamin C in the urine depends primarily on the relative degree of saturation of the tissues and the immediate intake of vitamin C. The quantity of ascorbic acid in the urine has been used in a variety of ways as a measure of the state of vitamin C of the tissues and the presence or absence of a state of deficiency. However, single specimens of urine may vary so widely in content of vitamin C that the determinations are valueless. The determination of vitamin C in twenty-four specimens of urine has other disadvantages.

The mechanisms by which the kidney excretes vitamin C are those of glomerular filtration and active tubular reabsorption, according to Ralli, Friedman and Rubin,<sup>190</sup> who have stated that the excretion of vitamin C is determined by (1) the plasma level, (2) the rate of glomerular filtration and (3) the maximal rate of tubular reabsorption.

Bessey<sup>188</sup> is of the opinion that rapid direct application of the titration method of determining the content of vitamin C in the blood will for many purposes undoubtedly replace the less practical technic of determining this substance in collected specimens of urine. By means of a single determination of the blood the reserve of vitamin C can be estimated for persons in that wide zone between scurvy and saturation (0.3 and 1.8 mg. per hundred cubic centimeters of blood).

Ascorbic acid is a threshold substance, and Faulkner and Taylor<sup>191</sup> have reported that the critical level of excretion is in the vicinity of 1.4 mg. per hundred cubic centimeters of serum. A blood value of ascorbic

189 Hand, D. B., Guthrie, E. S., and Sharp, P. E. Effect of Oxygen, Light and Lactoflavin on Oxidation of Vitamin C in Milk, *Science* **87**:439-441 (May 13) 1938.

190 Ralli, E. P., Friedman, G. J., and Rubin, S. H. The Mechanism of the Excretion of Vitamin C by the Human Kidney, *J. Clin. Investigation* **17**:765-770 (Nov.) 1938.

191 Faulkner, J. M., and Taylor, F. H. L. Observations on the Renal Threshold for Ascorbic Acid in Man, *J. Clin. Investigation* **17**:69-75 (Jan.) 1938.



acid maintained at or above this threshold level corresponds to the so-called saturated state, while values below this correspond to the unsaturated state

As Wright<sup>192</sup> has stated, "Probably the simplest procedure giving the maximum amount of information is a single determination of cevitamic acid in the blood plasma" The normal level for cevitamic acid in blood plasma for adults lies between 0.7 and 1.3 mg per hundred cubic centimeters

It is of interest to note that the blood of the umbilical cord of the human fetus at birth has a content of vitamin C which is two to four times or even more (average, 1.3 mg) that of maternal plasma taken at the time of delivery As suggested by Teel and his associates,<sup>193</sup> who made this finding, these figures indicate that there is increased need for vitamin C during pregnancy and that the fetus acts parasitically, "taking what it needs irrespective of the mother" Similar findings have been noted by Manahan and Eastman<sup>194</sup>

The values for vitamin C in the spinal fluid parallel closely those for vitamin C in the blood Wortis, Liebmann and Wortis<sup>195</sup> have shown that if the blood content is above 0.7 mg per hundred cubic centimeters, the value for the spinal fluid is almost invariably normal, however, if the value for the blood is less than 0.4 mg, the spinal fluid value is invariably subnormal

*Diagnosis of Vitamin C Deficiency*—A discussion of the large number of procedures which have been described as having value in the diagnosis of vitamin C deficiency would be beyond the limits of this review Wright<sup>196</sup> has recently reviewed these various methods and has presented a critical analysis of them

Of particular interest to clinicians should be an evaluation of various tests of capillary resistance or fragility and of the intradermal test which has recently been described Tests of this type can be performed simply, while, on the other hand, the determination of vitamin C in the blood

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192 Wright, I. S. Cevitamic Acid (Ascorbic Acid, Crystalline Vitamin C) A Critical Analysis of Its Use in Clinical Medicine, *Ann Int Med* **12** 516-528 (Oct) 1938

193 Teel, H. M., Burke, B. S., and Diaper, R. Vitamin C in Human Pregnancy and Lactation, *Am J Dis Child* **56** 1004-1010 (Nov) 1938

194 Manahan, C. P., and Eastman, N. J. Cevitamic Acid Content of Fetal Blood, *Bull Johns Hopkins Hosp* **62** 478-481 (May) 1938

195 Wortis, H., Liebmann, J., and Wortis, E. Vitamin C in the Blood, Spinal Fluid and Urine, *J A M A* **110** 1896-1899 (June 4) 1938 Liebmann, J., Wortis, H., and Wortis, E. Note on Lack of Correlation of Capillary Fragility with Vitamin C Content of Blood, Spinal Fluid and Urine, *Am J M Sc* **196** 388-392 (Sept) 1938

196 Wright, I. S. The Present Status of the Clinical Use of Cevitamic Acid, *Am J M Sc* **192** 719-735 (Nov) 1936, footnote 192

requires considerable experience and laboratory equipment, and an intravenous test dose of 1,000 mg of vitamin C entails considerable expense

Increased fragility of capillaries when due to vitamin C deficiency with occasional exceptions will be restored to normal by the administration of this vitamin to the patient. Wright,<sup>192</sup> who has expressed the opinion that "in spite of all of our chemical procedures to determine saturation, fragility of the minute vessels still remains the first positive clinical measure of the presence of the disease entity—scurvy" This test is not specific, however, and may give positive results in a variety of conditions. Gothlin,<sup>197</sup> who has had much to do with establishing the usefulness of this test, still feels that it retains its clinical value, despite the development of direct chemical methods for the estimation of vitamin C. However, the relation between the number of petechiae which appear under standard conditions and the concentration of ascorbic acid in the blood is not sufficiently exact to permit quantitative predictions

The method of studying vitamin C saturation and of determining the presence or absence of vitamin C deficiency by means of test doses has been widely used, and there are many reports of various types of tests—the variation is principally in the size of the dose, the method of administration and the period during which the urine is collected for analysis. Wright<sup>192</sup> is of the opinion that a test dose of 1,000 mg introduced intravenously is the most satisfactory. Normally at least half of this dose is excreted during the following twenty-four hours, and of the 500 mg, 80 per cent appears in the urine within the first five hours. There may be several disadvantages in using such large test doses, for, as pointed out by van Eekelen and Heinemann,<sup>198</sup> intravenous administration of even modest doses or an intake by mouth of an excessively large dose at one time can simulate saturation by causing urinary excretion of a surplus before the depletion of the body has been overcome. Rall and Friedman<sup>199</sup> are included among those investigators who advocate an intravenous test dose of 100 mg.

Considerable interest was aroused by the suggestion that an intradermal dye test might be of value in the diagnosis of vitamin C deficiency. Portnoy and Wilkinson<sup>200</sup> reported that using the method described by

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197 Gothlin, G. F. When Is Capillary Fragility a Sign of a Subnormal Supply of Vitamin C in Man? *Acta paediat* **20** 71-94, 1937

198 van Eekelen, M., and Heinemann, M. Critical Remarks on the Determination of Urinary Excretion of Ascorbic Acid, *J Clin Investigation* **17** 293-299 (May) 1938

199 Rall, E. P., and Friedman, G. J. The Response to the Feeding of Cevitamic Acid in Normal and Deficient Subjects as Measured by a Vitamin C Excretory Test, *Ann Int Med* **11** 1996-2006 (May) 1938

200 Portnoy, B., and Wilkinson, J. F. Vitamin C Deficiency. An Intradermal Test, *Brit M J* **1** 328-329 (Feb 12) 1938

Rotter<sup>201</sup> they obtained results which suggested that the method was a useful, rapid clinical test for vitamin C subnutrition and worthy of further study. The test was based on the fact that since the determination of vitamin C is dependent on the reduction of a blue dye, 2, 6-dichlorophenolindophenol, to its leuco form, the possibility of study in the reduction of the dye by the vitamin C in the skin seemed possible. According to their observations, when decolorization of the dye injected intradermally occurs in less than five minutes, the result indicates saturation of the tissues with vitamin C, while if it occurs in ten minutes or longer, the evidence favors the presence of deficiency of vitamin C. However, Poncher and Stubenrauch<sup>202</sup> were unable to confirm these results and suggested that the data obtained by them indicated that the intradermal dye test in its present form cannot be relied on to give satisfactory clinical information as to the ascorbic acid saturation in the individual case. Wright and MacLenathen<sup>203</sup> also have carefully checked this method and found it unsatisfactory, since the range of error is too great.

Vauthey<sup>204</sup> has reached the conclusion that the "basic ascorburia," a term he applies to the hourly excretion of vitamin C in the urine while the patient is fasting, may be regarded as a physiologic constant and that it may be employed to determine the vitamin C content of the organism or for the detection of latent hypovitaminosis C.

Mělka and Klímo<sup>205</sup> made observations on the vitamin C content of the spinal fluid in 277 cases and found that the detected values were of no diagnostic significance in distinguishing normal persons from those with disorders of the central nervous system.

*Relation of Vitamin C to Diseases of the Joints and to Peptic Ulcer*—Vitamin C deficiency has been related to a large variety of diseases, despite the fact, as Finkle<sup>206</sup> has pointed out, that a low body level of vitamin C is the cause of no other disease but scurvy, with the possible exception of lupus erythematosus.

201 Rotter, H. Determination of Vitamin C in the Living Organism, *Nature*, London **139** 717 (April 24) 1937, *Bestimmung des Vitamins C im lebenden Organismus*, *Wien klin Wchnschr* **51** 205-206 (Feb 18) 1938.

202 Poncher, H. G., and Stubenrauch, C. H., Jr. Intradermal Dye Test for Vitamin C Deficiency, *J. A. M. A.* **111** 302-304 (July 23) 1938.

203 Wright, I. S., and MacLenathen, E., cited by Wright<sup>192</sup>.

204 Vauthey, M. Etudes sur le métabolisme de la vitamine C: valeurs de l'ascorburie de base au cours du métabolisme normal, *Arch d mal d l'app digestif* **28** 230-235 (March) 1938, abstracted, *J. A. M. A.* **110** 1963 (June 4) 1938.

205 Mělka, J., and Klímo, Z. Ascorbinsäuregehalt in der Cerebrospinalflüssigkeit des Menschen, *Klin Wchnschr* **17** 302-303 (Feb 26) 1938.

206 Finkle, P. Vitamin C Saturation Levels in Body in Normal Subjects and in Various Pathological Conditions, *J. Clin Investigation* **16** 587-593 (July) 1937.

The observation of Rinehart and his associates<sup>207</sup> that the vitamin C level of the blood plasma during fasting is almost uniformly and severely lowered in rheumatoid arthritis and rheumatic fever was interpreted by them as affording significant support for the thesis that chronic deficiency of vitamin C is an important factor in the causation of these diseases. However, a majority of other investigators in discussing this work are not in agreement with this opinion. Keith and Hickmans,<sup>208</sup> who have made a more recent contribution to this subject, found no direct evidence to support the theory that rheumatic fever is a manifestation of vitamin C deficiency associated with an infection.

The interesting problem of the possible relation of peptic ulcer to deficiency of vitamin C and more particularly of hemorrhage from an ulcer to deficiency of vitamin C remains unsolved. Portnoy and Wilkinson<sup>209</sup> have reported careful studies of a group of 107 subjects (51 controls, 25 patients with ulcer and 31 with hematemesis) on whom six methods for determining vitamin C nutrition were studied, based on urinary excretion, the saturation test, the initial plasma values, tolerance for ascorbic acid given orally, tolerance for ascorbic acid given intravenously and the intracutaneous test. According to all these tests, patients with peptic ulcer, especially those with bleeding, presented evidence suggestive of vitamin C deficiency. Almost all other workers, for instance, Rivers and Carlson,<sup>210</sup> Ingalls and Warren,<sup>211</sup> Bourne<sup>212</sup> and Chamberlin and Perkins,<sup>213</sup> agree that patients with peptic ulcer, even those receiving an approved diet for ulcer, have lower levels of ascorbic acid in the blood and urine than have normal persons. However, as

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207 Rinehart, J. F., Greenberg, L. D., Baker, F., Mettier, S. R., Bruckman, F., and Choy, F. Metabolism of Vitamin C in Rheumatoid Arthritis, *Arch. Int. Med.* **61** 537-551 (April) 1938. Rinehart, J. F., Greenberg, L. D., Olney, M., and Choy, F. Metabolism of Vitamin C in Rheumatic Fever, *ibid.* **61** 552-561 (April) 1938.

208 Keith, J. D., and Hickmans, E. M. Vitamin C Excretion in Children with Particular Reference to Rheumatic Fever, *Arch. Dis. Childhood* **13** 125-136 (June) 1938.

209 Portnoy, B., and Wilkinson, J. F. Vitamin C Deficiency in Peptic Ulceration and Hematemesis, *Brit. M. J.* **1** 554-560 (March 12) 1938.

210 Rivers, A. B., and Carlson, L. A. Vitamin C as a Supplement in the Therapy of Peptic Ulcer, *Proc. Staff Meet., Mayo Clin.* **12** 383-384 (June 16) 1937.

211 Ingalls, T. H., and Warren, H. H. Asymptomatic Scurvy: Its Relation to Wound Healing and Its Incidence in Patients with Peptic Ulcer, *New England J. Med.* **217** 443-446 (Sept. 9) 1937.

212 Bourne, G. Vitamin C Deficiency in Peptic Ulceration Estimated by the Capillary Resistance Test, *Brit. M. J.* **1** 560-562 (March 12) 1938.

213 Chamberlin, D. T., and Perkins, J. J. The Level of Ascorbic Acid in the Blood and Urine of Patients with Peptic Ulcer, *Am. J. Digest. Dis.* **5** 493-497 (Oct.) 1938.

Jones and his collaborators <sup>214</sup> have pointed out in their review of gastroenterology, it is highly probable that these findings represent the results of a deficiency secondary to the original ulcer condition, rather than that there is a causative relation to the formation of ulcer. The latter authors have stated that it is probable that the intelligent administration of vitamin C to patients with ulcer who show a lack of vitamin C is a rational therapeutic procedure. Chamberlin and Perkins <sup>215</sup> were unable to find any clinical evidence that ascorbic acid in doses large enough to maintain the excretion at a normal level was of any value in the treatment of patients with peptic ulcer with or without hemorrhage.

*Therapy with Vitamin C*—Treatment with vitamin C is generally simple. Foods rich in the vitamin form the basis for any therapeutic approach in most cases in which deficiency of vitamin C is suspected or found. Curative doses of crystalline preparations of the vitamin vary from 30 to 1,000 mg daily. Occasionally patients will be unable to absorb appreciable quantities of the vitamin from the gastrointestinal tract, and it may be necessary to administer the vitamin to them either intramuscularly (up to 100 mg) or intravenously. Overdosage is not harmful, as the toxicity of ascorbic acid is low. As Wright <sup>192</sup> has pointed out, most patients with scurvy can be cured with ascorbic acid. A few seem resistant to this substance, whereas they can be cured by the administration of large doses of lemon juice or the juice of other citric fruits.

Vitamin C therapy has been recommended also in the treatment of heart failure (Evans <sup>215</sup>), insomnia (Maurer and his associates <sup>216</sup>), diabetes (Pfleger and Scholl <sup>217</sup>), asthma (Hunt <sup>218</sup> and Hagiesco and his associates <sup>219</sup>), urticaria (Rosenberg <sup>220</sup>) and a variety of other conditions, but the value of ascorbic acid in these conditions and conditions other than scurvy remains to be demonstrated.

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<sup>214</sup> Jones, C. M., Urmey, T. V., Benedict, E. B., Clifford, M. H., and White, B. V. *Gastroenterology: A Review of the Literature from January 1937 to June 1938*, Arch. Int. Med. **62**: 652-718 (Oct.) 1938.

<sup>215</sup> Evans, W. *Vitamin C in Heart Failure*, Lancet **1**: 308-309 (Feb. 5) 1938.

<sup>216</sup> Maurer, S., Wiles, H. O., Schoeffel, E. W., and Fisher, M. L. *The Effect of L-Cevitamic Acid on Insomnia*, Illinois M. J. **74**: 84-85 (July) 1938.

<sup>217</sup> Pfleger, R., and Scholl, F. *Diabetes und Vitamin C*, Wien Arch. f. inn. Med. **31**: 219-230, 1937, abstracted, J. A. M. A. **110**: 246 (Jan. 15) 1938.

<sup>218</sup> Hunt, H. B. *Ascorbic Acid in Bronchial Asthma*, Brit. M. J. **1**: 726-727 (April 22) 1938.

<sup>219</sup> Hagiesco, D., Bazavan, G., Criscota, M., and Cioranescu, M. *Essais de traitement de l'asthme pulmonaire par l'acide ascorbique lévogyre (vitamine C)*, Presse méd. **46**: 1435-1438 (Sept. 28) 1938, abstracted, J. A. M. A. **111**: 1885 (Nov. 12) 1938.

<sup>220</sup> Rosenberg, W. A. *Vitamin C Deficiency as Cause of Urticaria*, Arch. Dermat. & Syph. **37**: 1010-1014 (June) 1938.

## VITAMIN D

*Chemistry and Physiology*—The antirachitic effect of vitamin D is possessed by at least ten different sterols, according to Bills<sup>221</sup>. The two most important of these sterols in medicine are activated ergosterol and activated 7-dehydrocholesterol. The vitamin D of viosterol, irradiated yeast and yeast milk is identical and consists of activated ergosterol and calciferol. On the other hand, 7-dehydrocholesterol appears to be the principal activatable sterol or provitamin in cholesterol, the chief sterol of animal fats. It therefore comprises the vitamin D present in irradiated milk, it is produced in the skin on exposure to ultraviolet radiation and it is probably the chief although not the only form of vitamin D in fish oils.

Heymann<sup>222</sup> has produced evidence from experiments on rats that the liver plays an important role in the antirachitic function of vitamin D. By producing impairment of hepatic function in rats by means of carbon tetrachloride or by ligation of the common bile duct, he found that from two to three and from ten to twelve times, respectively, as much vitamin D in the form of viosterol in oil given intramuscularly was necessary to cure experimental rickets as to cure rickets in control animals without hepatic damage. In another study Heymann<sup>223</sup> observed that vitamin D is excreted through the intestinal wall, particularly in the upper third of the small intestine, when it is given parenterally to dogs with obstruction of the common bile duct.

The exact function of vitamin D in relation to calcium and phosphorus metabolism and to the parathyroid glands is still not clear. In a review of the physiology of vitamin D, Shohl<sup>224</sup> pointed out that the main action of the vitamin is to increase the absorption of calcium and phosphorus or to diminish their intestinal excretion. In an effort further to elucidate this complicated and confusing problem, Albright and Sulkowitch<sup>225</sup> have recently reported careful metabolic studies on 4 patients. They have pointed out that of the two hypothesized fundamental actions of vitamin D to decrease the fecal excretion of calcium and to increase the urinary excretion of phosphorus, it should be noted that the former would tend to heal rickets and the latter would tend toward demineraliza-

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221 Bills, C. E. The Chemistry of Vitamin D, *J. A. M. A.* **110** 2150-2155 (June 25) 1938.

222 Heymann, W. Metabolism and Mode of Action of Vitamin D. III. Importance of the Liver for Its Antirachitic Efficacy, *Am. J. Dis. Child.* **55** 913-923 (May) 1938.

223 Heymann, W. Metabolism and Mode of Action of Vitamin D. V. Intestinal Excretion of Vitamin D, *J. Biol. Chem.* **122** 257-262 (Dec.) 1937.

224 Shohl, A. T. Physiology and Pathology of Vitamin D, *J. A. M. A.* **111** 614-619 (Aug. 13) 1938.

225 Albright, F., and Sulkowitch, H. W. The Effect of Vitamin D on Calcium and Phosphorus Metabolism. Studies on Four Patients, *J. Clin. Investigation* **17** 305-315 (May) 1938.

tion of bone On the basis of the values for serum calcium and phosphorus, they hypothesized three types of vitamin D deficiency

(a) Normal calcium and a low phosphorus—where parathyroid hyperplasia has not occurred, (b) normal calcium and a low phosphorus—where parathyroid hyperplasia has compensated for low calcium and (c) low calcium, low phosphorus—where parathyroid hyperplasia has occurred but is unable to compensate for low calcium

*Requirement of Vitamin D*—The requirement of vitamin D may be defined, according to Jeans and Stearns,<sup>226</sup> as the amount which, with an ample intake of calcium and phosphorus and a diet otherwise adequate, will insure sufficient retention of calcium and phosphorus to permit (a) normal growth and mineralization of the skeleton and teeth of infants and children, (b) maintenance of bony and dental structures during adult life and (c) a sufficient supply for mother and infant during pregnancy and lactation

The Council on Foods of the American Medical Association<sup>227</sup> recently investigated the matter of the vitamin D requirement of premature infants and found that there is evidence that prevention of rickets in premature infants may be accomplished by administration of about 70 U S P units of vitamin D per kilogram of body weight However, for adequate retention of calcium and phosphorus and for growth it is concluded that from 600 to 800 U S P units of vitamin D fed in dispersed form will satisfy the requirements This is approximately twice the requirement for prevention of rickets and for growth of the majority of full term infants The Council noted that the claim be recognized that infants receiving customary quantities of milk containing 400 U S P units of vitamin D per quart exhibit good growth

For adolescents a need for vitamin D exists, but according to Jeans and Stearns,<sup>226</sup> insufficient data are available to permit an estimate of the quantity required An estimate of 300 to 400 U S P units daily is suggested For adults the optimal amount of vitamin D, if a need exists, remains to be determined During pregnancy and lactation 800 U S P units or more is suggested

*Treatment with Vitamin D*—The prevention and treatment of rickets have become greatly simplified since vitamin D has been available in the form of cod liver oil concentrate and vitamin D milk Almost all pediatricians and physicians have developed or accepted methods of therapy which have proved to be highly effective An excellent summary of this subject has been prepared by Park<sup>228</sup> An interesting contribution

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226 Jeans, P C, and Stearns, G The Human Requirements of Vitamin D, J A M A **111** 703-711 (Aug 20) 1938

227 Annual Meeting of the Council on Foods, report of the Council on Foods, J A M A **111** 156-157 (July 9) 1938

228 Park, E A The Use of Vitamin D Preparations in the Prevention and Treatment of Disease, J A M A **111** 1179-1187 (Sept 24) 1938

in this connection and one which at the same time should provoke physiologic discussion of the function of vitamin D is that of Braulke<sup>229</sup> concerning *Vitaminstoss* therapy. In 1935 Harnapp discovered accidentally that a single large dose of vitamin D produced prompt and rather lasting effects in healing rickets. Braulke advanced the technic of this method of therapy, gave it its name and reported the results of its use in 50 cases with no ill effects. He administered in a single dose about 15 mg of calciferol (600,000 U S P units of vitamin D) as compared to an ordinary dose of 3,000 U S P units. Within a few days healing was noted in roentgenograms, and the process proceeded to completion without further treatment. He feels that there are indications for using this method of therapy (1) in manifest and latent tetany, (2) in

TABLE 3—*Daily Requirements of Vitamins*

	Infant and Child	Adult	Pregnancy and Lactation	Suggested Optimal Amount for Adults	Therapeutic Doses
Vitamin A, U S P units	6,000 8,000*	2,000 4,000†	5,000+*	8,000 10,000	10,000 60,000
Vitamin B <sub>1</sub>					
International units	200 250†	200 500 <sup>138</sup>	600 700 <sup>143</sup>	500	2,500 15,000
Milligrams	1 0-1 5†	1 2 <sup>138</sup>	2 5-3 <sup>143</sup>	2	10-60
Nicotinic acid, mg	?	?	?	?	200 500 <sup>168</sup>
Riboflavin, mg	?	?	?	2 3 <sup>168</sup> (suggested)	?
Vitamin B <sub>6</sub>	?	?	?	?	?
Vitamin C, mg	40 100 <sup>185</sup>	50-100 <sup>185</sup>	60 100 <sup>185</sup>	80 100 <sup>185</sup>	25 3,000
Vitamin D, U S P units	400-600§	?	800 1,000 <sup>226</sup>	?	400 1,000,000

\* Report on the Physiological Bases of Nutrition, by the Technical Commission appointed by the Health Committee, League of Nations, Publication C H 1197, Geneva, Switzerland, World Peace Foundation, 1935

† Report by the Technical Commission on Nutrition on the Work of Its Third Session, Bull Health Organ, League of Nations 7 460 (June) 1938

‡ Report by the Technical Commission on Nutrition on the Work of Its Third Session, Bull Health Organ, League of Nations 7 461 (June) 1938, cited by Baker, A Z Human Requirements for Vitamin B<sub>1</sub>, J A M A 111 1866 (Nov 12) 1938

§ For the premature infant 600 to 800 U S P units<sup>227</sup> and for the growing child 300 to 400 U S P units<sup>226</sup> daily

moderate and severe rickets with acute or chronic infection, (3) in rachitis gravis and (4) in cases in which the likelihood of adequate treatment at home is unsatisfactory

A variety of dissimilar clinical conditions have been treated with massive doses of vitamin D. There has been little change in the status of this type of therapy in chronic arthritis during the past year. Abrams and Bauer<sup>230</sup> have summarized their experiences in this regard by

229 Braulke, H. Die Indikationen der Rachitisbehandlung mit einmaliger Dosis von Vitamin D<sub>2</sub> (Vitaminstoss), Ztschr f Kinderh 59 18-31, 1937, abstracted, Am J Dis Child 56 643-644 (Sept) 1938

230 Abrams, W R, and Bauer, W. The Treatment of Rheumatoid Arthritis with Large Doses of Vitamin D, J A M A 111 1633-1639 (Oct 29) 1938



stating that the results they have obtained indicate that the administration of massive doses of vitamin D in rheumatoid arthritis is of little or no value in alleviating the cause of the disease and does not justify the expense and dangers involved

Concerning cases of psoriasis, Ceder and Zon<sup>231</sup> have presented some interesting observations. In a series of 15 patients with widespread chronic psoriatic lesions to whom was given from 300,000 to 400,000 U S P units of vitamin D daily, these observers have reported that 11 showed complete involution of the lesions within six to twelve weeks. After cessation of the treatment there was recurrence of the lesions in some of the cases, although the degree of severity of the lesions was much less than was observed before. Care must be used to avoid producing evidence of hypervitaminosis D with this form of treatment.

Maynard<sup>232</sup> has reported encouraging results in the treatment of acne with doses of viosterol varying from 20 to 40 drops daily. Knapp<sup>233</sup> is of the opinion that keratoconus, a rare disease of the eye, can be reproduced in rats and dogs with diets deficient in vitamin D and calcium. He gave vitamin D and calcium to 11 patients with the disease and was able to produce gratifying results in all instances. However, Laval<sup>234</sup> was unable to confirm previously made observations that vitamin D and calcium help patients who have myopia by reducing the amount of myopia, by keeping it stationary or by preventing as rapid an increase in the process as is usually found in patients who have not used this form of therapy.

*The Treatment of Parathyroid Tetany with Dihydrotachysterol* — One of the most troublesome, even though infrequent, complications of surgical treatment of diseases of the thyroid gland is postoperative tetany. A majority of the patients have responded satisfactorily to administration of calcium, vitamin D and parathyroid extract. However, in all cases this type of therapy has not been successful. In the past year MacBryde<sup>235</sup> has reported an even more successful therapeutic agent, namely, dihydrotachysterol, which is a derivative of viosterol. By employing it orally in an oily solvent (5 mg per cubic centimeter), MacBryde reported that for the first time he had been able to maintain

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231 Ceder, E. T., and Zon, L. Treatment of Psoriasis with Massive Doses of Crystalline Vitamin D and Irradiated Ergosterol. Preliminary Report, Pub Health Rep **52** 1580-1584 (Nov 5) 1937

232 Maynard, M. T. R. Vitamin D in Acne. Comparison with X-Ray Treatment, California & West Med **49** 127-132 (Aug) 1938

233 Knapp, A. A. Vitamin D Complex in Keratoconus, J. A. M. A **110** 1993-1994 (June 11) 1938

234 Laval, J. Vitamin D and Myopia, Arch. Ophth. **19** 47-53 (Jan) 1938

235 MacBryde, C. M. The Treatment of Parathyroid Tetany with Dihydrotachysterol, J. A. M. A **111** 304-307 (July 23) 1938

patients with chronic tetany free from symptoms and to maintain the calcium content of the blood at normal levels. Dihydrotachysterol alone will raise the serum calcium value to normal, but daily doses of 1 to 2 cc are necessary if no calcium is added to the usual diet. By supplementing the diet with calcium lactate or gluconate in doses of 4 to 10 Gm a day, approximately normal levels of serum calcium can be maintained with doses of from 0.3 to 1 cc of dihydrotachysterol daily. After the administration of this substance the first increase in the calcium value occurs in about forty-eight hours, and in seven to fourteen days normal levels are reached. Pickhardt and Bernhard<sup>236</sup> have also reported excellent results with dihydrotachysterol in the treatment of 5 patients with tetany following an operation on the thyroid. The mechanism of action of the sterol is not clear as yet, but so far as is known the results of therapy persist only so long as the treatment is continued. Excessive doses produce hypercalcemia and severe toxic effects.

Albright and his associates<sup>237</sup> have studied the action of dihydrotachysterol and vitamin D on the calcium and phosphorus metabolism of 3 patients with hypoparathyroidism. They are of the opinion that the two substances have the same fundamental action, namely, to increase the absorption of calcium from the intestinal tract and to increase the excretion of phosphorus in the urine. The ratio of the latter action to the former, however, was apparently greater with dihydrotachysterol than with vitamin D, which may explain why dihydrotachysterol is not antirachitic. The action of parathyroid extract resembled that of dihydrotachysterol as regards its property of causing a markedly increased urinary excretion of phosphorus but differed in that it probably had no primary action on the absorption of calcium from the intestinal tract.

#### DENTAL CARIES

The occurrence of dental caries is so widespread and the disorder leads to so much discomfort and ill health that it is surprising that more attention is not paid to the problem, particularly by physicians. There are in essence two schools of thought in regard to the fundamental causes of dental caries—one which believes that the disease is the result of inadequate nutrition of the individual or of his teeth and the other which believes that the important etiologic factor is the environment of the teeth in the mouth, particularly in regard to the occurrence of con-

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236 Pickhardt, O. C., and Bernhard, A. Treatment of Postoperative Tetany with Dihydrotachysterol, *Ann Surg* **108** 362-373 (Sept.) 1938.

237 Albright, F., Bloomberg, E., Drake, T., and Sulkowitch, H. W. A Comparison of the Effects of A.T. 10 (Dihydrotachysterol) and Vitamin D on Calcium and Phosphorus Metabolism in Hypoparathyroidism, *J Clin Investigation* **17** 317-329 (May) 1938.

ditions which make it possible or impossible for organisms to infest the mouth and to produce acid Koehne,<sup>238</sup> who has been much interested in this problem, recently summarized the known facts in regard to it so well that her conclusions deserve repetition in a place where physicians may see them

1 It has been impossible to produce caries in most experimental animals Its recent production in rats was brought about by dietary conditions affecting the environment of the molars

2 Not all teeth in the mouth are equally susceptible

3 Cavities begin in highly protected areas on the outside of the tooth

4 Not all poorly enameled teeth are susceptible to caries

5 Not all well-enameled teeth are free from caries

6 Some persons are free from caries even though their diets have long been very inadequate nutritionally

7 Other persons are susceptible to caries even though they have long been accustomed to well-balanced diets

8 Caries can be produced in persons on well-balanced diets by additions to the diet of such a nature that their only known measurable effect is the increase in concentration of aciduric organisms in the saliva

The nutritional adequacy or inadequacy of the diet may be a factor in determining the rate of progress of caries, but is probably not its primary etiologic agent Saliva may contain a factor or factors that minimize the effect of acid formed on the tooth surface The nature of this factor is not yet known

The nature of true immunity is not yet known It is doubtless an inherited characteristic There is evidence that it inhibits the growth of certain aciduric micro-organisms in the body

There are many legitimate reasons for recommending that the diet of children and adults be nutritionally adequate If, at the same time, the use of concentrated sweets is reduced to an absolute minimum, there is the greatest likelihood that the incidence of caries in the civilized population of the world will be reduced to a minimum

#### VITAMIN E

References to vitamin E are to be found in the literature principally in journals dealing with biochemistry and with obstetrics and gynecology Internists have been unable to find clinical usefulness for it

Several substances, including alpha and beta tocopherol, have vitamin E activity Evans and the Emersons<sup>239</sup> reported during the past year that the feeding of durohydroquinone and of various of its esters and certain cyclic ethers indicates that vitamin E activity is displayed by some of these substances when fed at high levels Synthetic alpha-

238 Koehne, M Relation of Diet to Oral Health, *J Am Dent A* 25 1767-1780 (Nov) 1938

239 Evans, H M, Emerson, G A, and Emerson, O H The Chemistry of Vitamin E II Biological Assays of Various Synthetic Compounds, *Science* 88 38-39 (July 8) 1938

tocopherol was as effective as the same substance secured from natural sources

Shute<sup>240</sup> and more recently Currie<sup>241</sup> have reported the favorable effects of vitamin E in wheat germ oil on patients with habitual abortion, and the former author has suggested that vitamin E and estrogen or a substance much like it exist in a sort of equilibrium in pregnancy. If there is too much of the estrogenic substance, the pregnancy is terminated.

The presence of a neurotropic factor in wheat germ oil and the effect of chronic vitamin E deficiency on the nervous system and the skeletal musculature of adult rats are the subjects of a monograph by Einarson and Ringsted<sup>242</sup>

#### VITAMIN K

There has been much interest during the past year in a possible relation between deficiency of vitamin K and the hemorrhagic tendency in jaundice. This substance or group of substances, which originally was associated only with a hemorrhagic disease in chicks, has risen to clinical interest because of observations of a deficiency of prothrombin in the plasma of chicks with vitamin K deficiency and of dogs and of men with various diseases of the biliary tract and liver.

As Snell, Butt and Osterberg<sup>243</sup> have pointed out, a deficiency of prothrombin occurs in chicks fed on diets lacking in certain fat-soluble substances, in experimental animals with external or renal biliary fistulas, in dogs whose livers have been injured by chloroform and in cattle fed on toxic sweet clover hay. They believe two factors, the presence of bile in the bowel and the presence of a hypothetic fat-soluble vitamin, are of importance in maintaining a normal concentration of prothrombin in the blood. A third and equally important factor is that which has to do with the fabrication, storage or activation of prothrombin, which apparently occurs in the liver. If these hypotheses are correct, the most likely causes of prothrombin deficiency and therefore of the hemorrhagic tendency in jaundice are failure of absorption of vitamin K in adequate amounts and interference with the metabolism of prothrom-

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240 Shute, E. Early Diagnosis of Abruptio Placentae and Its Treatment with Wheat Germ Oil, *Am J Obst & Gynec* **33** 429-436 (March) 1937

241 Currie, D. Vitamin E in Treatment of Habitual Abortion, *Brit M J* **2** 1218-1220 (Dec 18) 1938

242 Einarson, L., and Ringsted, A. Effect of Chronic Vitamin E Deficiency on the Nervous System and Skeletal Musculature in Adult Rats. A Neurotropic Factor in Wheat Germ Oil, translated by H. Andersen, New York, Oxford University Press, 1938

243 Snell, A. M., Butt, H. R., and Osterberg, A. E. The Treatment of the Hemorrhagic Tendency in Jaundice, with Special Reference to Vitamin K, *Am J Digest Dis* **5** 590-596 (Nov) 1938

bin as a result of hepatic damage Smith and his associates<sup>244</sup> have recently shown that in the absence of bile in the intestines, fat-soluble vitamin K is poorly absorbed

Further evidence of the importance of the liver in this problem is indicated by a recent report of Lichtman and Chambers,<sup>245</sup> who were able to obtain evidence indicating that the liver contains a sterol which is active in reducing the clotting time of the blood of normal and jaundiced dogs The extract was similar in action to vitamin K but differed from it in several clinical properties

Snell and his associates<sup>243</sup> have not observed an abnormal tendency to bleed in any jaundiced patient with a normal prothrombin value To what degree must the prothrombin level fall before the hemorrhagic tendency appears? Warner, Brinkhous and Smith<sup>246</sup> have suggested that for the dog this critical condition occurs when the prothrombin reaches a level of 20 to 30 per cent of the normal content As long as the content of prothrombin remains above this point, no marked prolongation of coagulation time occurs This observation may explain why patients with jaundice at times bleed abruptly and unexpectedly, for a small loss of prothrombin by a patient whose plasma content is near the "critical" level might presumably bring the level below the point required for the formation of a clot

The effects of administering vitamin K to more than 30 patients have been reported by Butt and his associates<sup>247</sup> They used concentrates prepared from putrefied fish meal or extracted from alfalfa together with bile salts or human bile Apparently when administered to jaundiced patients by mouth vitamin K must be accompanied by bile or bile salts to be absorbed Administration of these two substances to patients who have jaundice has been followed by an elevation in the quantitative level of prothrombin in the circulating blood and by a reduction in the elevated prothrombin clotting time, and in 13 cases actual bleeding has been controlled

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244 Smith, H P , Warner, E D , Brinkhous, K M , and Seegers, W H Bleeding Tendency and Prothrombin Deficiency in Biliary Fistula Dogs Effect of Feeding Bile and Vitamin K, *J Exper Med* **67** 911-920 (June) 1938

245 Lichtman, A L , and Chambers, W H Reduced Blood Coagulation Time by Injection of Sterol Extract of Liver, *Science* **88** 358-359 (Oct 14) 1938

246 Warner, E D , Brinkhous, K M , and Smith, H P A Quantitative Study on Blood Clotting Prothrombin Fluctuations Under Experimental Conditions, *Am J Physiol* **114** 667-675 (Feb) 1936

247 Butt, H R , Snell, A M , and Osterberg, A E Further Observations on the Use of Vitamin D in the Prevention and Control of the Hemorrhagic Diathesis in Cases of Jaundice, *Proc Staff Meet, Mayo Clin* **13** 753-764 (Nov 30) 1938

The desirability of using a preparation of vitamin K which may be given parenterally is obvious, particularly for use in those cases in which because of injury to the liver large amounts of the vitamin are required to obtain the desired effect. Emulsions of the vitamin have been used intramuscularly by Dam and Glavind,<sup>248</sup> with return to normal of the clotting power of the blood of 5 patients who had obstructive jaundice and deficiency of blood coagulation. However, Butt, Snell and Osterbeig<sup>247</sup> have reported that the concentrates which they used intramuscularly did not effectively alter extremely high prothrombin levels, although they are of the opinion that this method of administration may be of some prophylactic use after operation.

Almquist<sup>249</sup> and Doisy and his collaborators<sup>250</sup> have reported obtaining vitamin K in crystalline form. The latter observers<sup>251</sup> have also reported that minute amounts of vitamin K permit complete recovery within a few days from the anemia which accompanies vitamin K deficiency.

#### OTHER SO-CALLED VITAMINS AND ESSENTIAL SUBSTANCES

*Vitamin F*—Certain essential unsaturated fatty acids, such as linoleic acid, have been called vitamin F by some investigators. Burr and his associates<sup>252</sup> made further studies of these substances and found that the human subject requires preformed unsaturated fatty acid in the diet and that arachidonic acid is effective as a curative agent in relieving the condition which is caused by deficiency of essential unsaturated fatty acids. It is suggested by the observations of Turpeinen<sup>253</sup> that at least two double bonds appear necessary for fatty acids to be effective in curing "fat deficiency" disease, these double bonds must occupy the position 9-10 and 12-13 to possess the features which are responsible for the curative properties of an eighteen carbon atom fatty acid.

248 Dam, H., and Glavind, J. Clotting Power of Human and Mammalian Blood in Relation to Vitamin K, *Acta med Scandinav* **96** 108-128, 1938.

249 Almquist, H. J. Further Studies on the Anti-Hemorrhagic Vitamin K, *J Biol Chem* **120** 635-640 (Sept.) 1937.

250 Thayer, S. A., MacCorquodale, D. W., Binkley, S. B., and Doisy, E. A. The Isolation of a Crystalline Compound with Vitamin K Activity, *Science* **88** 243 (Sept. 9) 1938.

251 Thayer, S. A., McKee, R. W., MacCorquodale, D. W., and Doisy, E. A. Recovery from the Anemia Caused by a Diet Deficient in Vitamin K, *Proc Soc Exper Biol & Med* **37** 417-480 (Nov.) 1938.

252 Brown, W. R., Hansen, A. E., Burr, G. O., and McQuarrie, I. Effects of Prolonged Use of Extremely Low Fat Diet on Adult Human Subject, *J Nutrition (supp)* **15** 13 (June) 1938. Burr, G. O., Kass, J. P., Brown, J. B., and Frankel, J. On the Fatty Acids Essential in Nutrition, *ibid* **15** 15 (June) 1938.

253 Turpeinen, O. Further Studies on the Unsaturated Fatty Acids Essential in Nutrition, *J Nutrition* **15** 351-366 (April) 1938.

*Vitamin P*—There is a divergence of opinion in regard to the existence of vitamin P, also known as citrin or the vitamin of permeability (described by Szent-Gyorgyi<sup>254</sup>) Lajos,<sup>255</sup> who believes the substance is a mixture of glucosides that belong to the group of the flavones, has reported favorable results in arresting the hematuria of hemorrhagic nephritis with citrin Jersild<sup>256</sup> has reported the favorable response of a young woman with Schonlein-Henoch purpura to the use of citrin

Zilva<sup>257</sup> and others do not believe that the vitamin exists

*Vitamin M*—Day, Langston and Darby<sup>258</sup> have described a deficiency syndrome observed in monkeys and characterized by anemia, leukopenia and loss of weight, with ulceration of the gums and diarrhea They have reported that this syndrome could be prevented by administration of liver extract or yeast but not by the use of moderate doses of riboflavin, nicotinic acid or thiamin They have termed the unknown etiologic factor vitamin M

*Anti-Gizzard-Erosion Factor*—Additional evidence regarding this substance has been presented by Cheney<sup>259</sup> and by Bird and Oleson<sup>260</sup> The latter authors found that chondroitin exerted a marked protective action against lesions of the gizzard when fed to chicks at a level of 3 to 5 per cent of the ration Preparations of greater purity appeared to be more potent than crude preparations

Since the report by Dam<sup>261</sup> of the occurrence of erosions in the gizzard of chicks with hemorrhagic disease, there has been speculation of the possible relation of the anti-gizzard-erosion factor to vitamin K Further support for the idea that they are separate substances is given in the work of Almquist<sup>262</sup>

254 Bentsáth, A, Rusznyak, S, and Szent-Gyorgyi, A Vitamin P, *Nature*, London **139** 326-327 (Feb 20) 1937

255 Lajos, S Klinische Erfahrungen mit "Citrin" (Vitamin "P"), *Klin Wchnschr* **16** 1615-1617 (Nov 13) 1937, abstracted, *J A M A* **110** 245 (Jan 15) 1938

256 Jersild, T Therapeutic Effect of Vitamin P in Schonlein-Henoch Purpura, *Lancet* **1** 1145-1447 (June 25) 1938

257 Zilva, S S Vitamin P, *Biochem J* **31** 915-919 (June) 1937

258 Day, P L, Langston, W C, and Darby, W J Failure of Nicotinic Acid to Prevent Nutritional Cytopenia in the Monkey, *Proc Soc Exper Biol & Med* **38** 860-863 (June) 1938

259 Cheney, G Gastric Acidity in Chicks with Experimental Gastric Ulcer, *Am J Digest Dis* **5** 104-107 (April) 1938

260 Bird, H R, and Oleson, J J Effectiveness of Chondroitin as the Anti-Gizzard Erosion Factor Required by Chicks, *J Biol Chem* **123** 211-211 (May) 1938

261 Dam, H Cholesterinstoffwechsel in Huhnereiern und Huhnchen, *Biochem Ztschr* **215** 475-492, 1929

262 Almquist, H J Influence of Bile Acids on Erosions of the Chick Gizzard Lining, *Science* **87** 538 (June 10) 1938

## THE INCIDENCE AND DIAGNOSIS OF VITAMIN DEFICIENCY STATES

Classic examples of well established deficiency diseases, with the exception of rickets and pellagra, are uncommon in this country. However, it is becoming generally agreed that mild states of suboptimal nutrition or borderline states of partial deficiency are common (Minot<sup>263</sup>). It is in conditions of this type that clinical recognition is difficult, because the deficiency is due principally to biochemical or physiologic rather than to pronounced pathologic alterations.

General and sweeping statements regarding the widespread presence or absence of deficiency diseases are made not infrequently but are difficult to prove or disprove. A Committee on Nutritional Problems of the American Public Health Association has recently issued a report on this subject entitled "Extent of Vitamin Deficiency in the United States"<sup>264</sup>. The report consists chiefly of a discussion of various measures which have been suggested as diagnostic procedures for determining vitamin deficiency and of a discussion of some of the pathologic changes accompanying these deficiency states. There is surprisingly little and in fact almost no information in this report concerning the extent of vitamin deficiency in this country. The absence of such data fairly well summarizes available information on the subject.

An editorial<sup>265</sup> in a recent issue of *The Journal of the American Medical Association* states that, in general, studies of problems relating to the incidence of vitamin deficiency states indicate that deficiency of vitamin D and deficiency of calcium are more frequent than that of any other nutritional element. There also seems to be an increasing amount of both clinical and experimental evidence that deficiency of vitamin B<sub>1</sub> may be more common than previously believed.

The situation in regard to the problem in Great Britain is summarized by a former chief officer of the Ministry of Health, who is quoted as saying that the British are better fed than at any period in their history, that there is no doubt room for improvement and that the diet is overweighed with energy-giving foods instead of protective foods.<sup>266</sup>

The potentiality of a race which consumes a diet rich in protective foods seems to be tremendous. The problems which confront any effort made to secure general distribution of protective foods include not

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<sup>263</sup> Minot G R Nutritional Deficiency, *Ann Int Med* **12** 429-442 (Oct) 1938

<sup>264</sup> Extent of Vitamin Deficiency in the United States, report of the Committee on Nutritional Problems, American Public Health Association, *Am J Pub Health* (supp) **28** 75-80 (Feb) 1938

<sup>265</sup> Normal Nutrition, editorial, *J A M A* **111** 1846 (Nov 12) 1938

<sup>266</sup> What Is Wrong with the British Diet? *Foreign Letters* (London), *J A M A* **109** 2149 (Dec 25) 1937



only those related to nutrition but also those related to economics, finance and racial likes, dislikes and prejudices. As Simmonds<sup>267</sup> has stated, nutrition may now be considered largely a problem of economics and education, and she adds that there is too much of a tendency to discuss nutrition in terms of vitamins, essential amino acids, carotene, thiamin chloride, ascorbic acid, nicotinic acid, dicalcium phosphate, calcium gluconate, units of various vitamins in foods and units of various vitamins needed daily by individuals, whereas to prevent unnecessary confusion the question of a balanced nutrition must be discussed in terms of milk, meat, potatoes, carrots, oranges and cod liver oil. Magee,<sup>268</sup> in discussing this problem at the recent International Physiology Congress in Zurich, emphasized other phases of the subject and then deplored the application of experimental work in the laboratory to mass problems of human nutrition (in India, for example). Leake,<sup>269</sup> in the same discussion, suggested that biochemists might examine the logic of their recommendations in nutrition, particularly in regard to the use of maximal effects on size and weight as the best criteria of biologic excellence.

The diagnosis of vitamin deficiency states presents an important but difficult problem to the clinician. The early general symptoms of nutritional deficiency are vague, as Minot<sup>263</sup> has pointed out, and consist of a sense of fatigue or lack of energy, inefficiency, mental irritability, mild anemia and simple disorders of the digestive tract. The symptoms and signs of deficiency may be referable to the bones, to faulty growth, to the neural, blood-forming and reproductive systems, and to the skin. However, such indefinite symptoms are common in a large variety of diseases. In an effort to obtain objective evidence substantiating a clinical diagnosis of a vitamin deficiency state or in establishing this diagnosis in the absence of specific clinical symptoms, a variety of diagnostic procedures has been suggested. These methods are well summarized in a report of the proceedings of a round table discussion on nutrition and public health at the sixteenth annual conference of the Milbank Memorial Fund<sup>270</sup> and in a series of lectures by Ungley,<sup>271</sup>

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267 Simmonds, N. Recent Research in Nutrition in Relation to Preventive Medicine, *J A M A* **111** 1073-1076 (Sept 17) 1938, The Dietary History and Its Value in Dental and Medical Practice, *Am J Digest Dis & Nutrition* **4** 497-503 (Oct) 1937.

268 Magee, cited in International Nutritional Problems, editorial, *J A M A* **111**:1569 (Oct 22) 1938.

269 Leake, C D, cited in International Nutrition Problems, editorial, *J A M A* **111** 1569 (Oct 22) 1938.

270 Nutrition. The Newer Diagnostic Methods, Proceedings of the Round Table on Nutrition and Public Health, New York, Milbank Memorial Fund, 1938.

271 Ungley, C C. Some Deficiencies of Nutrition and Their Relation to Disease. I. Origin and Detection of Nutritional Deficiencies, *Lancet* **1** 875-882 (April 16) 1938.

published in the *Lancet*. In various parts of this review will be found reports from the literature discussing the evaluation of some of these "diagnostic" procedures.

#### SUMMARIES OF INFORMATION OF IMPORTANCE IN NUTRITION

During the past year there have appeared several books, round table discussions and a series of articles on the vitamins of much value to those interested in the field of nutrition. In *The Journal of the American Medical Association* there has appeared an excellent series of articles on vitamins which have been prepared under the general auspices of the Council on Pharmacy and Chemistry and the Council on Foods. The first article appeared in *The Journal* for Feb. 18, 1938, and the series will be published later in book form. Of value also is a statement appearing in the 1938 edition of *New and Nonofficial Remedies* as to the claims allowed for the vitamins in preventive medicine and in therapeutics. These claims represent a summary of the present knowledge.

The volume by Williams and Spies<sup>138</sup> entitled "Vitamin B<sub>1</sub> and Its Use in Clinical Medicine" is a valuable discussion of chemical, physiologic and clinical phases of this subject. Of interest particularly to those in the experimental field is a book by Katherine S. Coward,<sup>272</sup> "Biological Standardization of the Vitamins." In this excellent work are discussed vitamins A, B<sub>1</sub>, C and D, because they are the only vitamins for which international units and standards have so far been set up.

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<sup>272</sup> Coward, K. S. *Biological Standardization of the Vitamins*, London, Baillière, Tindall & Cox, 1938.

## News and Comment

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**Symposium on Public Health Significance of Virus and Rickettsial Diseases**—The faculty of the Harvard School of Public Health offers a short course of lectures, clinics and demonstrations on virus and rickettsial diseases, with special emphasis on their public health significance, to be held at the school during the week of June 12 to 17, 1939. Lectures on the etiology, epidemiology and methods of control of these diseases, given by members of the faculties and by former students of the Harvard School of Public Health and of the Harvard Medical School, will occupy five mornings. Special clinics and demonstrations will be continued through the week, so that all the members of the symposium can attend. On the last morning a panel discussion will be held on the three main topics presented in the symposium.

The fee for the course will be \$25, payable at any time up to June 12. Enrolment, however, should be arranged before June 1, as facilities for many of the clinics and demonstrations are limited. The lectures will be published later in a single volume, which will be sent to each person who registered for the course.

Further information may be had by writing to the secretary of the School of Public Health, 55 Shattuck Street, Boston.

**The 1939 Journées médicales de Bruxelles**—The eighteenth session of the Journées médicales de Bruxelles will be held in Liege, Belgium, June 24 to 28, under the presidency of Prof. Ernest Renaux, member of the Académie royale de Médecine.

The scientific program will comprise scheduled authoritative lectures on medical questions, practical demonstrations and operative sessions in the hospitals, and there will be numerous social diversions, as well as excursions to Spa and to the Albert Canal, which has recently been completed.

For information and enrolment, address the secretary, Dr. René Beckers, 141 Rue Belliard, Brussels, Belgium.

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### CORRECTION

In the article by Dr. Stanley Cobb, "Review of Neuropsychiatry for 1938," in the November issue (*ARCH. INT. MED.* 62:883, 1938), in the twelfth line from the bottom of page 884 the word "centimeter" should read "millimeter", i. e., "White matter has about 200 to 300 mm of capillary length per cubic millimeter of brain substance, while gray matter has from 600 to 1,000 mm."

## Book Reviews

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**Internships and Residencies in New York City, 1934-1937 Their Place in Medical Education** Report by the New York Committee on the Study of Hospital Internships and Residencies, Jean Alonzo Curran, M.D., Executive Secretary Price, \$2.50 Pp 492 New York The Commonwealth Fund, 1938

The educational opportunities of internships in general have been the subject of much discussion, especially by the Council on Medical Education and Hospitals of the American Medical Association. Stimulated by the new standards for qualification of specialists established by the medical specialty boards, serious consideration is now being given to the educational opportunities provided by the hospital residency.

In the present volume appear the results of investigations of a committee organized by five medical colleges of New York and the New York Academy of Medicine. The factual material was assembled by Dr. Curran and subjected to study by a group of men who for the most part are engaged in medical education. It seems that the city of New York offers more than one sixth of all the internships and residencies of the entire country. Students from all parts of the United States receive training in these positions, and thus these hospitals not only provide a large sampling of the problem of intern residency of the country at large but by example exert a great influence on hospital education everywhere.

Only a few of the many important deductions arrived at by the committee can be mentioned. The preparation of graduates of American and Canadian medical schools is regarded as adequate and, in general, distinctly superior to that provided by foreign schools. With few exceptions men trained abroad fit poorly into the American scheme. Frequently, however, the hospital fails to give new interns adequate instruction regarding their responsibilities and duties, and thus slipshod methods and careless procedure are encouraged. Measured by the quality of medical examinations and by the teaching of technics, much remains to be done to place the internship on a thoroughly satisfactory educational basis. Training in the outpatient department is given the lowest rating.

It was found that the provision of residencies in hospitals distinctly elevates the quality of medical service as well as improves the teaching given to interns and students. The residencies, moreover, are providing opportunities for special training in the basic sciences and other essentials required for the qualification of specialist. This is true, however, only when the appointments are of two years' duration or longer. The standing of residencies in existence should be raised, especially those in surgery need bolstering in quality. Residencies in obstetrics and gynecology enjoy the highest rating, while those in medicine occupy an intermediate position.

The most serious deficiency found in the hospital staffs is a deficit of trained teachers. Little formal effort is made by members of the profession to qualify its members in the art of teaching, and not infrequently the instructing of interns and even of medical students is delegated to physicians who have no understanding of how to organize teaching schedules or to insure the educational progression of their charges. The development of residencies on a truly educational basis offers an opportunity to meet this deficiency. "All thoughtful and forward-looking studies of hospital internships and residencies must arrive at the same conclusion—that their primary and essential function is educational. While they serve a useful purpose in the care of the sick in the modern highly-organized hospital, it is only by this practical, supervised experience that the student doctor can be qualified to assume independent responsibility for the care of patients."

This investigation undoubtedly will do much to improve the training of physicians. The work of the committee is to be continued, with the plan of making new surveys from time to time, thus serving as a source of information regarding graduate medical education for those who are responsible for the guidance of students.

**The Therapeutic Problem in Bowel Obstruction** By Owen H. Wangensteen  
Price, \$6 Pp 360, with 90 illustrations Springfield, Ill Charles C Thomas,  
Publisher, 1937

The publication of this monograph has been made possible by the author's well deserved reception of the Samuel D. Gross prize. In brief, it is a concise but thorough exposition of the more "important aspects of the therapeutic problem in obstruction of the bowel" in the light of the vast investigations and experience of the writer and his co-workers.

The text is divided into three parts. The first section is devoted to a succinct but complete elaboration of the altered physiologic state and the pathologic consequences of obstruction and distention of the bowel, which are clearly demonstrated by the extensive clinical and experimental investigations of the author and his collaborators. On this basis is built the evident rationale and therapeutic efficacy of the administration of saline solution in high obstruction, conservative decompression by suction applied to a duodenal tube, blood transfusion and operation. The second portion of the text consists of a dissertation on the considerations of diagnosis and treatment in cases of obstruction. The criteria for early recognition and differentiation of acute abdominal disorders are lucidly evaluated, and a critical analysis of the therapeutic value of various agents and of the choice of operative procedures is made. The third part is concerned primarily with a classic, textbook description of the accepted facts characterizing the various special types of intestinal obstruction due to congenital atresia, imperforate anus, tumor, stricture, hernia, volvulus, intussusception and other causes.

This compendium may be considered a valuable addition to the modern library of the internist as well as that of the surgeon, not only because it is a thorough exposition of the pathologic physiology and the therapeutic considerations of intestinal obstruction but also because it represents the most recent progress yet made in the management of a condition as perplexing as it is serious. Because in great measure this progress has been due to the important contributions of the author and his co-workers, the book is even more valuable.

**Man Against Himself** By Karl A. Menninger Price, \$3.75 Pp 485 New York Harcourt Brace and Company, Inc., 1938

Under this intriguing title there comes from Dr. Menninger's pen another popular work on psychiatry. This time the subject is suicide—thoroughly analyzed, documented with case reports, correlated with "slow suicide" (asceticism) and finally set off in its relations to the "living suicide" type of neurosis. Dr. Menninger writes plausibly, he is clearly a master of exposition in his subject. The inherent motive of self destruction side by side with that of self preservation, the suicide of the banker not because his speculations were discovered but because his mother was hard to him in his childhood, the repressed housewife who refused to go out because she wanted to hurt her husband, whom she really loved but could not resist torturing—all this is exposed and analyzed with admirable clearness. None the less, the reviewer—probably through ignorance—is not convinced at all points. To take one example, the concept of nail biting as a prelude to devouring one's fingers, in other words, self destruction, seems a little far fetched in most cases. Surely many people gnaw their finger nails when nervous just as they twiddle a rubber band or make random scratch marks with a pencil. Does this require an esoteric interpretation? Again, as in the review of Dr. Menninger's previous book, the question is raised as to whether such a treatise is good popular medicine, whether those who need treatment can get it profitably in this way or

will not rather be confused, and whether those who are of reasonably sound mind benefit from material which (to paraphrase Poe) contains much of the wanton, much of the bizarre, something of the terrible and not a little of that which might excite disgust

**Milestones in Medicine** With an introduction by James A. Miller Price, \$2  
Pp 276 New York D. Appleton-Century Company, Inc., 1938

This would be a delightful present for one of those many laymen who are interested in medicine or for a young man on the threshold of his premedical course or, for that matter, for a well read practitioner of medicine. Each would find in the volume many interesting new facts.

There are curious facts about the beginnings of psychiatry in Greece in ancient times and even more curious facts about the genes and the ways in which they are now being studied and located in giant chromosomes. Vogel's chapter describing the awful dietary, medical and hygienic conditions which existed on ships in olden times is one of the most interesting in the book. When it is learned how the sailors had to live on stinking water, rotten salt pork and moldy hardtack, it can readily be seen why sometimes half the sailors on a man-of-war died of diarrhea and scurvy.

Tilney gives a brief resumé of what has been learned lately about the intelligence of monkeys and apes. Sigerist writes about the development of the science of medical history. Wayson reviews the history of leprosy and throws light on the questions of why this scourge was so common in Europe in the Middle Ages and why later it disappeared. Doubtless in many cases the diagnosis was wrong. Interesting is Wayson's suggestion that some of the lesions may have been due to ergotism and to the partial starvation which was so common in the Middle Ages. In the last chapter Timme gives a brief but interesting and sane résumé of what is known about the glands of internal secretion.

**Men Past Forty** By A. F. Niemoeller, M.A. Pp 154, with 6 illustrations  
New York Harvest House, 1938

This little booklet dealing with impotence and rejuvenation in fairly simple, easy language is obviously intended for the layman, although it may be read with profit by the average practitioner. The reader is adequately admonished to consult only reputable physicians and specialists and to avoid the quack preparations and appliances advertised in sensational magazines. The author is inclined to agree with Steckel and his disciples that psychic impotence greatly predominates over the so-called secondary organic or physiologic form. This point of view undoubtedly will be shared by the majority of the members of the medical profession. The medical treatment and the psychotherapeutics of the condition are outlined. The aphrodisiac yohimbine alone or in combination with various other preparations is favored. The author also lists a number of the foreign and domestic preparations of aphrodisiac and organotherapeutic nature and their manufacturers. The organotherapy and surgical treatment of rejuvenation are discussed with proper conservatism. The volume closes with a brief chapter on the menopause in men and includes Dr. Lorand's "twelve commandments" for avoiding premature old age, which are largely injunctions for hygienic living.

**A Diabetic Manual** By Elliott P. Joslin Sixth edition, thoroughly revised  
Price, \$2 Pp 219, with 49 illustrations Philadelphia Lea & Febiger, 1937

Protamine zinc insulin has opened another door to the diabetic patient. In the sixth edition of the "Diabetic Manual" Dr. Joslin makes available to both physician and patient the most recent methods of using this long-acting insulin intelligently and effectively. The advantages and disadvantages of the use of protamine zinc insulin as they appear at present are given in detail.

The chapter on diabetic children is most interesting and dramatic. Here are emphasized the necessity for education of the child and the importance of yearly

adjustments in his diet to take care of normal growth as well as activity. Helpful suggestions and instructive tables relative to dietary calculations and the planning of the menu form an important part of this valuable book.

The book covers the subject of diabetes well and gives all the essential information necessary for the intelligent care of the patient. Education of the patient is the keynote of this manual.

**Pneumonia and Serum Therapy** By Frederick T. Lord and Roderick Heffron. Revised edition. Price, \$1. Pp 148, with 10 illustrations and 10 tables. New York: The Commonwealth Fund, 1938.

This little book is an ideal summary of the recent developments in the typing of pneumococci and in serum therapy. A vast amount of information scattered throughout the literature has been assembled, with practical directions about procedure. The tables and charts are particularly valuable, and the physician has ample material from which to draw his own conclusions as to whether serum therapy is indicated in an individual case.

**Verhandlungen der deutschen Gesellschaft für Kreislaufforschung, Volume 140** Edited by Prof. Dr. Eberhard Koch. Price, 15 marks. Pp 320, Dresden: Theodor Steinkopff, 1937.

In this well printed and profusely illustrated volume are reported the papers read at the 1937 meeting of the German society for the study of the circulation. The material is miscellaneous and does not lend itself to review in brief space. There are many interesting articles by authorities on various aspects of the circulation.

**Anniversary Volume. Scientific Contributions in Honor of Joseph Hersey Pratt on His Sixty-Fifth Birthday** By His Friends. Price, \$7. Pp 983. Lancaster, Pa.: Lancaster Press, Inc., 1937.

This *Festschrift*, as appears from the title, contains a collection of papers by various authors. The subjects, like Dr. Pratt's own activity, range over the entire field of the science, practice, history and teaching of medicine. The contributors number one hundred and twenty. The separate papers have already been published in the *Annals of Internal Medicine*.

**Traitement chirurgical du cancer du côlon pelvien** By Pierre Bertrand and E. Corajod. Price, 30 francs. Pp 208, with 36 illustrations. Paris: Masson & Cie, 1936.

This little volume follows the French manner of dealing in monographic style with a narrow subject. The work is really an enlarged textbook article and covers the subject adequately, but it adds nothing fundamental. The illustrations are poor.

**Nuevos estudios sobre los neumotórax espontáneos** By Mariano R. Castex and Egidio S. Mazzei. Pp 164. Buenos Aires: "El Ateneo," 1937.

This small book deals with spontaneous pneumothorax and its chief causes. The authors differentiate between blebs, bullae, recurrent pneumothorax and tuberculosis as causative agents. The book is well worth while for those who are interested in the subject and can read Spanish.

**Síndrome adiposo genital** By Luis Viamonte Cuervo. Pp 62, with 30 illustrations. Habana: Seoane, Fernandez y Cia, 1937.

This is a brief presentation of a quite common syndrome. The work is largely a report of a series of cases plus a fairly extensive review of the literature, for the most part of the Latin countries.

## HEMOCHROMATOSIS

REPORT OF A CASE WITH NECROPSY AND ANALYSIS OF THE LIVER

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AND

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In his monograph on hemochromatosis (1935) Sheldon<sup>1</sup> accepted from the literature 311 cases of the disease. The incidence of hemochromatosis found at necropsy has been reported by Rowen and Mallory<sup>2</sup> as 0.05 per cent in a series of 6,500 autopsies. Blanton and Healy<sup>3</sup> reported finding the condition at 0.08 per cent of 5,000 autopsies at Bellevue Hospital. The postmortem incidence reported from other sources ranged between 0.001 and 0.4 per cent. The diagnosis of the disease is made more often at autopsy than clinically, owing to the fact that pigmentation has been the factor which suggested the diagnosis. That cutaneous pigmentation is not an essential criterion for the diagnosis of hemochromatosis is well known. The four cardinal signs of the disease occur, according to Sheldon, in the following order: (1) enlargement of the liver (92 per cent), (2) pigmentation (84 per cent), (3) diabetes mellitus (78 per cent) and (4) genital hypoplasia, which is characterized by impotence and loss of secondary hair.

We shall report a case of hemochromatosis which was under observation from the time of onset of symptoms until death, eleven weeks later.

### REPORT OF CASE

V. H., a 39 year old Irishman, entered the wards of the Third (New York University) Medical Division, Bellevue Hospital, on the night of Sept. 4, 1936, complaining of weakness and loss of 16 pounds (7.3 Kg.) during the preceding two weeks and vomiting for the preceding three days. During this period there had been a marked loss of appetite, and the diet had been totally inadequate. The patient was a paint mixer and for twelve years had been exposed to zinc, lead and arsenic. He had had malaria in 1915, there was a history of alcoholism, and

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1 Sheldon, J. H. Hemochromatosis, London, Oxford University Press, 1935.

2 Rowen, H. S., and Mallory, F. B. Am J Path 1: 677, 1925.

3 Blanton, W. B., and Healy, W. Hemochromatosis, Arch Int Med 27: 406 (April) 1921.



he had been admitted to another hospital in 1929, after a four day attack of abdominal cramps, vomiting and diarrhea

On admission, physical examination showed that the patient was normally developed and rather poorly nourished, and appeared chronically ill (fig 1) The temperature was 99 F There was no respiratory distress A marked odor of acetone on the breath was noted There was a dusky appearance of the skin of the face, hands and legs The head was normal, save for telangiectasis over both cheeks Examination of the eyes showed the pupils, conjunctivas and scleras



Fig 1—Appearance of the patient on Oct 29, 1936, showing absence of secondary hair, protrusion of abdomen (ascites) and edema of the abdominal wall The lower border of the liver is outlined

to be normal Examination of the ears, nose and throat showed the teeth and gums to be in poor condition There was no lead line The tongue was dry The neck was normal, with no masses The thyroid gland was not palpable The lungs were clear throughout The point of maximum intensity of the heart beat was diffuse in the fifth intercostal space, inside the midclavicular line The sounds were of good quality The aortic and the pulmonic second sound were equal There were no thrills, gallop or rub The rhythm was of the regular sinus type The pulse rate was 90 The blood pressure was 125 systolic and 90 diastolic There was a sense of fulness in the epigastrium The edge of the

liver was felt 4 fingerbreadths below the costal margin and extended diagonally to the left upper quadrant. The edge was firm, sharp, irregular and nontender. The spleen was not felt. There was no fluid wave or shifting dullness. There were no superficial dilated veins. Cyanosis was present over the upper and lower extremities. There was no edema or clubbing. Neurologic examination showed no abnormality. There was complete absence of secondary hair, save for a sparse beard.

Urinalysis on admission showed a volume of 600 cc, 39 Gm of sugar and 4 plus reactions for acetone and diacetic acid. The sugar content of the blood was 570 mg per hundred cubic centimeters and the carbon dioxide-combining power was 25 volumes per cent. The diagnosis on admission was (1) diabetes mellitus with ketosis and (2) cirrhosis of the liver.

Treatment for diabetic ketosis was begun. After a gastric lavage with a solution of sodium bicarbonate, an infusion of 5 per cent dextrose in physiologic solution of sodium chloride was started and insulin given. The patient's condition remained good, and six hours after admission urinalysis showed a small amount of sugar and a faint reaction for acetone. During this period the patient received 3,500 cc of physiologic solution of sodium chloride, 185 units of insulin and 175 Gm of dextrose. For the remainder of the night the patient was fed orange juice, and small doses of insulin were given. Sixteen hours after admission the carbon dioxide-combining power of the blood was 55 volumes per cent.

Other laboratory data on admission were 4,670,000 red blood cells, 100 per cent, or 14.5 Gm, of hemoglobin, and 6,900 white blood cells, with a normal differential count and smear. The Wassermann reaction was negative, urinalysis showed no abnormality save for the presence of sugar and ketone bodies.

The morning after admission the patient was in good condition and was given a diet of 250 Gm of carbohydrate, 80 Gm of protein and 85 Gm of fat in six feedings, with 15, 10, 10, 10, 10 and 10 units of insulin, respectively, at each feeding. It was observed that the dusky appearance noted the night before was due to a bluish gray "slate" color, which was most marked over the face and extremities but was also present over the rest of the body. The diagnosis of hemochromatosis was suggested.

#### COURSE IN THE HOSPITAL

*First Period*—The patient was soon able to eat three regular meals a day. An additional feeding of orange juice and insulin was given at midnight. He remained in good condition for about four weeks. During this period various diagnostic procedures were performed. Roentgen examination of the heart and lungs and the stomach and intestines, gastric analysis and proctoscopic examination showed no abnormality. Electrocardiograms taken early in the course and later showed no change. There was no deviation of the electrical axis, the PR interval and QRS complex were of normal duration, QRS waves were slurred in leads I and II, the T wave was diphasic in lead II and inverted in lead III. The rhythm was of the regular sinus type, with auricular premature contractions. Communication with the hospital to which the patient was admitted in 1929 verified his occupational history. The report stated that there was "a peculiar cyanosis of his entire body. The liver was enlarged and the spleen palpable."

A bromsulphalein excretion test one week after admission (September 11) showed 5 per cent retention of the dye at the end of one-half hour. A biopsy specimen of skin taken during this period showed "a moderate deposition of pigment which stained brown with hematoxylin and eosin and blue with the prussian blue stain. The diagnosis was hemochromatosis."

During this period of well-being the patient was on a diet of 275 Gm of carbohydrate, 80 Gm of protein and 85 Gm of fat. His insulin requirement fell from 115 units a day early in September to 60 or 75 units a day the next month (fig 2). Slight glycosuria was permitted. There were no hypoglycemic reactions.

*Second Period*—During October, after the patient had been in the hospital for five weeks, ascites and edema of the lower extremities first made their appearance (October 12). At this time the albumin-globulin ratio was 3:2.5. A bromsulphalein test (October 28) showed 100 per cent retention of the dye after one-half hour. Proctoscopic examination again revealed a normal mucous membrane. Ascites progressively increased, but was never distressing. The patient lost 7 pounds (3.2 Kg.) after one intravenous injection of 2 cc of mercupurin (a mercurin-theophylline preparation). The second period of four weeks (after the appearance of the ascites) was characterized by minor complaints, notably epigas-

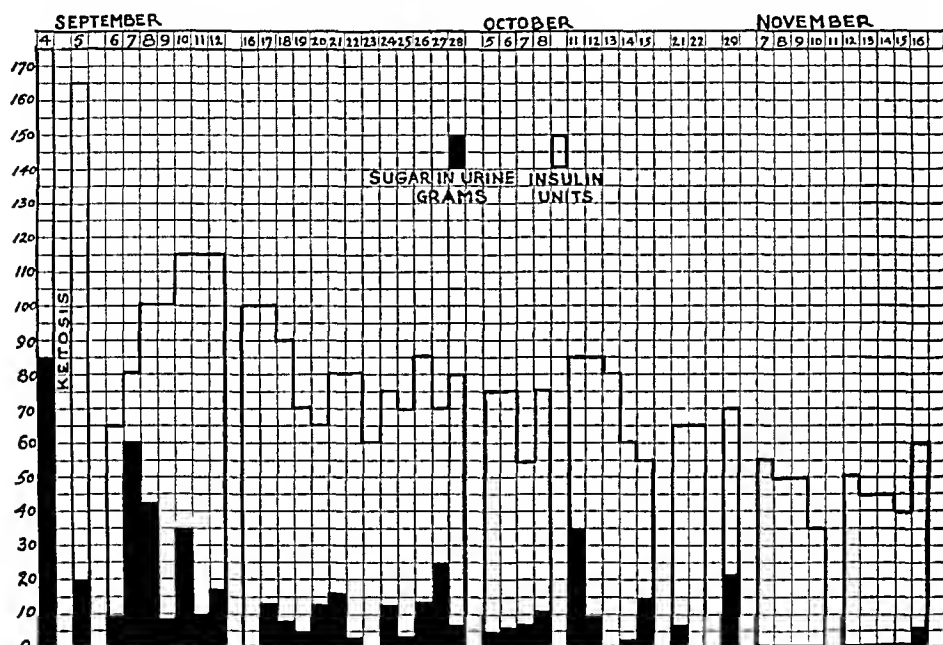


Fig 2—Chart showing the insulin requirement and degree of glycosuria during hospitalization

tric distress and nausea, but these were never more than mild. The same diet was continued, and approximately the same doses of insulin. There was no apparent change in the cutaneous pigmentation. On October 22 a drop in the red blood cells, to 3,800,000, with 90 per cent, or 126 Gm, of hemoglobin, was noted. The only qualitative change in the blood smear was the presence of a few round macrocytes. The white blood cell count was normal. The van den Bergh reaction was negative, and the icterus index was not elevated. No methemoglobin was found in the blood. An analysis of the urine showed the presence of 0.05 mg of lead in 1,300 cc. The examination of the urinary sediment showed the presence of intracellular iron-containing pigment. The diet during this period had been augmented by 1 drachm (3.88 Gm) of Vegex three times a day and 1 fluidrachm (37 cc) of iron and ammonium citrates (50 per cent solution) three times a day.

*Terminal Period*—The last week of the patient's illness was ushered in by a severe attack of diarrhea, which lasted but one day. There was no evidence of

ketosis, and the patient was apparently well the next day. Three days later it was noted that the veins in the neck were distended, but did not pulsate or fill from below. There was edema of the anterior wall of the chest. A gallop rhythm was heard over the precordium. There was no clinical evidence of enlargement of the heart. Electrocardiograms taken at this time showed no change from the preceding ones. Determinations of the sugar content of the blood on three days during the last week showed 250 mg per hundred cubic centimeters, at 2 p m, 216 mg, at 2 p m, and 180 mg, at 4 30 p m. The carbon dioxide-combining power on the day before death was 47.5 volumes per cent.

On the day before death edema spread over the entire body to include the face. Vomiting, dyspnea and cyanosis were moderate. Mild ketosis was treated successfully with intravenous injections of dextrose and small doses of insulin. Abdominal paracentesis was performed, without relief. The terminal episode was one of pulmonary and cerebral edema, with the development of left hemiplegia. Intravenous injection of hypertonic solutions produced no relief. Examination of the throat revealed no evidence of edema of the larynx. The insulin requirement during this period is shown in the chart (fig 2). The downward course was rapid, with marked pulmonary edema. The patient died on November 18, eleven weeks after admission. The final diagnosis was hemochromatosis and diabetes mellitus.

#### NECROPSY REPORT

*Macroscopic Examination*—The external features given were confirmed at the postmortem table. When the abdomen was opened about 3 liters of clear sanguineous fluid was found in the peritoneal cavity. The edge of the liver extended 8 cm below the right costal margin and 12 cm below the xiphoid process. It completely covered the spleen in the left upper quadrant. Each pleural cavity contained about 1 liter of serosanguineous fluid. There was marked congestion of both lungs and the trachea and bronchi. The heart weighed 400 Gm. There was moderate dilatation of all chambers, particularly the right ventricle. The superior and the inferior vena cava were normal. There were no gross abnormalities. The arterial system was thin walled and natural throughout. The aorta was normal save for scattered yellowish plaques in the abdominal portion, measuring 3 or 4 mm. The liver weighed 3,500 Gm. Its capsular surface was purplish brown and glistening, but slightly nodular, the individual nodules measuring 2 or 3 mm in diameter. The liver cut with slightly increased resistance, presenting a bright brown surface which was diffusely nodular. The original hepatic nodules could not be recognized. The spleen weighed 450 Gm. The pulp was deep red, and numerous follicles could be seen in its substance. The pancreas was altered considerably in appearance. The color was deep chestnut brown and the substance firm. In some areas the lobulations could not be made out. The stomach presented a deep brown surface, with many submucosal pinhead-sized areas of hemorrhage. Similar changes were observed in the duodenum and the first 3 feet (90 cm) of the jejunum. Scattered areas of submucosal hemorrhage were seen throughout the remainder of the gastrointestinal tract. The kidneys showed multiple infarcts and fetal lobulations. The adrenal glands appeared normal in size. The medulla appeared cystic, and the cortex was discolored a greenish brown. The thyroid gland, testes and bladder appeared normal. A brownish coloration was noted in the left lobe of the prostate. The lymph nodes along the abdominal aorta and about the pancreas were a deep chestnut brown and of normal size. The brain showed no abnormalities grossly.

*Microscopic Examination*—Liver There was considerable distortion of the hepatic pattern. Thick, dense layers of fibrous tissue surrounded the portal zones, breaking the hepatic tissue into small nodules. Many of the hepatic cells were well preserved, but there were many areas of atrophy, particularly in the central portions of the lobules. Large amounts of brown-yellow iron-containing pigment were present, with numerous macrophages within the fibrous stroma. This pigment in less coarse form was seen within the polygonal and Kupffer cells. A few bile ducts contained pigment. The diagnosis was hemochromatosis and portal cirrhosis (pigment).

Lungs Several brown-pigmented iron-containing macrophages were seen within the alveoli. A few small bronchioles contained uniform iron pigmentation, and many small irregular deposits of hemosiderin were present within the walls of the arteries. The diagnosis was slight hemochromatosis and patchy atelectasis.

Pancreas The lobular structure was preserved, but changes were present within the individual lobules. A somewhat increased stroma was seen along the course of the acini, which varied in density, in some portions merely separating and elsewhere breaking up and replacing the cells. Embedded in the stroma were many large and small macrophages in which there was much iron-containing pigment in coarse granules. The acinar cells also contained pigment, but in lesser amounts. The islets of Langerhans appeared decidedly less numerous than normal. They were generally free from pigmentary and other changes. The arterioles showed slight hyaline thickening. The diagnosis was hemochromatosis with slight intralobular pigmentary cirrhosis and arteriosclerosis.

Thyroid Most of the follicles were large and filled with colloid. There was considerable yellow-brown iron-containing pigment within the follicular epithelioid cells and to a much less extent in the capillary walls. Small particles were infrequent within the stroma, although most of the latter was free from pigment.

Spleen Yellow-brown iron-containing pigment was seen in many macrophages within the lymphoid deposits and pulp, in the trabecular elements and arterial walls and to a lesser extent within the pulp stroma. The diagnosis was hemochromatosis and chronic passive congestion.

Myocardium The fibers appeared increased in width, and there were diffuse deposits of particles of coarse brown iron-containing pigment within the bundles. Pigment was present within many macrophages between the fibers. There was slight focal intrafascicular fibrosis. The aorta was normal. The diagnosis was hemochromatosis and focal intrafascicular fibrosis.

Kidneys In the noninfarcted areas the structure was normal. Iron stains showed deposition of pigment within the cells of the tubules, particularly the loops of Henle, and there was a slight amount in the glomerular tufts. The diagnosis was slight hemochromatosis and multiple infarctions with beginning organization.

Stomach The mucosal and glandular cells were heavily laden with iron-containing pigment. The plial epithelial cells of the jejunum were only slightly stained.

Adrenal Glands The structure was normal. There was considerable deposition of iron-containing pigment, particularly in the outer layer of the cortex. The diagnosis was hemochromatosis.

Prostate Iron-containing pigment was present in the lining cells of many follicles and in the interstitial tissue. The diagnosis was hemochromatosis.

Testes The basement membrane was thickened. Many groups of tubules were fibrotic, and those which were still cellular failed to show evidence of complete

spermatogenesis In a few small blood vessels there was iron-containing pigment within the endothelial cells

Brain Section through the pons showed an area of necrosis on each side of the base, involving some of the fibers of the pyramidal tract These softened areas contained no phagocytes In places there were small perivascular hemorrhages, and in the fourth ventricle there was slight ependymitis such "as is seen sometimes in syphilis or alcoholism" The nature of these necrotic foci was not clear, but they were "probably due to occlusion of the small arteries" The diagnosis was bilateral areas of softening in the pons

#### COMMENT

Urine—(A) Hemosiderin Intracellular granules of hemosiderin were found in the urine in this case by the technic described by Rous<sup>4</sup> According to Sheldon,<sup>1</sup> use of this technic was mentioned in 10 reported cases and gave positive results in 8 When one considers the severity of tubular siderosis which may be found in this disease, it is not surprising that cast-off hemosiderin-bearing cells are present in the urinary sediment While a positive reaction to the test is not limited to this disease, the simplicity of a search for these granules suggests itself as a valuable adjunct in the verification of the diagnosis

(B) Melanin Uhlenbruck<sup>5</sup> described a case in which melanin was present in the urine No melanin was found in the urine in our case, although tests were made by the method of Haden and Orr<sup>6</sup> The cutaneous pigmentation in this disease has been ascribed to both melanin and hemosiderin by several authors Hellier<sup>7</sup> has shown the presence of these pigments in the skin in this disease In our case a biopsy specimen of skin of the lower part of the leg failed to reveal any increase in melanin, while hemosiderin was seen in abundance If the pigmentation were due to an increase in the production of melanin such as one finds in melanotic tumors, this might manifest itself by the presence of urinary melanin However, the absence of melanin in greater quantity than that found in normal skin, the slaty color of the skin and the absence of melanin in the urine all militated against an abnormality of melanin production as a factor in the case

(C) Porphyrins During the terminal period of the patient's illness the urine was examined for porphyrins by the method of Brugsch,<sup>8</sup> with negative results Coproporphyrin I or III was not demonstrated by the method of Dobriner<sup>9</sup> This is interpreted as additional evidence of acute hepatic insufficiency

4 Rous, P J Exper Med **28** 645, 1918

5 Uhlenbruck, P Deutsches Arch f klin Med **167** 80, 1930

6 Haden, R L, and Orr, T G Bull Johns Hopkins Hosp **35** 58, 1924

7 Hellier, F F Brit J Dermat **47** 1, 1935

8 Brugsch, J T Munchen med Wchnschr **81** 1546, 1934

9 Dobriner, K J Biol Chem **113** 1, 1936

*Ascitic Fluid*—The ascitic fluid revealed no hemosiderin in the cellular sediment obtained by centrifuging 200 cc and examined by the method used for urinary sediment, nor was there any melanin in this fluid when tested by the method of Haden and Orr <sup>6</sup>

*Pigments Present in Hemosiderosis*—In 1889 von Recklinghausen <sup>10</sup> described two pigments which were present in hemochromatosis (a) an iron-containing pigment, described previously by Neumann as hemosiderin, and (b) a noniron-containing pigment, hemofuscin. The first, hemosiderin, occurs in the secreting cells of the glands, the connective tissue of these glands, the lymph nodes, striated muscle, the cartilages and synovia and the walls of the blood vessels. This pigment occurs in fine single granules or granules clumped together in masses, varying from deep yellow to brown. The granules are angular, with a sharp outline. The pigment is insoluble in alkalis and soluble in acids <sup>11</sup>. Aniline dyes or alum hematoxylin does not stain the pigment, <sup>12</sup> but potassium ferrocyanide in acid medium stains the granules a blue green, which on heating becomes the prussian blue of the ferric ferrocyanide reaction. Potassium ferricyanide and potassium thiocyanate give no reaction <sup>11</sup>. There are points of dispute concerning the exact nature of the pigment, but the fundamental constitution is well established. Many observations have shown the presence of iron, and Sheldon credited Auscher and Lapique (1895-1898) with being the first to call the pigment a hydrated oxide of iron existing in combination with organic matter. This finding has been substantiated by Cook <sup>11</sup> and by Asher, <sup>13</sup> both working with horse spleen. Jacoby, <sup>14</sup> in a study of the liver of a patient with hemochromatosis, concluded that the iron was combined with protein.

While we carried out no detailed investigation, we attempted to elicit several reactions to show the nature of the pigment, and we were led to believe that the iron present existed in the ferric state and that it occurred with a non-iron moiety. Cook found that the hemosiderin consisted of an iron compound which could be removed from the granules by treatment with acid, leaving the substrate practically intact. This we, too, observed. Acid extracts yielded reactions similar to those described by Cook for potassium ferrocyanide, potassium thiocyanate and sodium hydroxide. However, our observations differed as to the behavior of tissue on direct application of ferrocyanide and ferricyanide in the presence of acid. We obtained a positive reaction for ferric iron

10 von Recklinghausen. Berl klin Wchnschr **26** 925, 1889

11 Cook, S. F. J Biol Chem **82** 595, 1929

12 Mallory, F. B., Parker, F., and Nye, R. N. J M Research **42** 461, 1920

13 Asher, T. Ztschr f phvsiol Chem **220** 97, 1933

14 Jacoby, M. Biochem Ztschr **230** 225, 1931

when ferrocyanide was applied, while Cook reported that the tissue required warming, in our experiments the tissue yielded Turnbull's blue with ferricyanide for ferrous iron, which was much fainter, however, than the reaction for ferric iron and may have been due to the fact that the examination was carried out several days post mortem, allowing for change of the original ferric iron

*Iron and Copper in the Liver and Spleen*—The increase of iron and copper in the various tissues in hemochromatosis has been amply confirmed. We analyzed the liver and spleen in our case by the method of Kennedy,<sup>15</sup> using a photoelectric colorimeter instead of the colorimeter specified by the author. The copper content was determined by the method of McFarlane,<sup>16</sup> except that the iron was removed by precipitation as the hydroxide.

Our results are listed in table 1, together with those of other authors for persons with similar diseases and for normal subjects. Ramage and

TABLE 1—*Iron and Copper Contents of the Liver and Spleen of Patients with Hemochromatosis and of Normal Subjects*

	Liver		Spleen	
	Iron, Gm per 100 Gm (Dry)	Copper, Mg per 100 Gm (Dry)	Iron, Gm per 100 Gm (Dry)	Copper, Mg per 100 Gm (Dry)
Our patient	2.33	6.5	0.56	8.3
Other patients	3.6 to 2.1	4 to 40	0.27 to 0.13	10.4
Normal subjects of various authors	0.05	2.5	0.14	2.7

Sheldon<sup>17</sup> determined the iron content of the liver and spleen by the method used by us, our method of copper determination differed from theirs.

From the composite data (table 1) the increase in iron and copper in the liver and spleen in this case is apparent.

*Vitamin A*—In 1935 Ralli and her associates<sup>18</sup> reported the vitamin A content of the liver in a case of hemochromatosis, with the findings in 7 cases of diabetes mellitus and in 13 cases in which diabetes was not present. The method of Cair and Price<sup>19</sup> was used in these determinations, in which the concentration of the vitamin is expressed in the blue units of the Lovibond tintometer. In the present case

15 Kennedy, R. P. *J Biol Chem* **74** 385, 1927.

16 McFarlane, W. D. *Biochem J* **26** 1022, 1932.

17 Ramage, H., and Sheldon, J. H., *Quart J Med* **4** 121, 1935.

18 Ralli, E. P., Brandaleone, H., and Mandelbaum, T. *J Lab & Clin Med* **20** 1266, 1935.

19 Carr, F. H., and Price, E. A. *Biochem J* **20** 497, 1926.



vitamin A was determined by the method of Davies,<sup>20</sup> with the Hilger vitameter, the results are expressed in U S P XI units. The value previously reported by Ralli for a patient with hemochromatosis was 1,905 blue units per hundred grams of liver, while the lowest found among patients with diabetes was 9,680 blue units and the corresponding figure for normal subjects was 8,800 blue units. The lowest value for a diabetic and a normal subject were thus five and four and one-half times as great as that of the patient with hemochromatosis. In a series of cases of chronic disease Wolff<sup>21</sup> reported the average value to be 20,600 blue units per hundred grams, while in a series of 25 cases of diabetes the average was 48,400 blue units per hundred grams. In a series of 6 cases of cirrhosis of the liver the average was 7,100 blue units per hundred grams, and the corresponding value in 3 cases of acute yellow atrophy was 14,700 blue units. The low value for the vitamin in cases of cirrhosis as contrasted to that in atrophy was

TABLE 2—*Lipids in the Liver of a Patient with Hemochromatosis*

	Percentage	Percentage of Total Lipids
Total lipids	4.97	
Unsaponifiable material	0.89	
Total fatty acids	3.40	
Iodine number fatty acids	95.0	
Lipid phosphorus	0.03	
Phospholipid	2.09	42
Cholesterol (free + total)	0.334	
Neutral fat	2.12	43

confirmed by Breusch and Scalabrino.<sup>22</sup> In our case the vitamin A content of the liver was 53 U S P XI units per gram of wet tissue. This value is the lowest found to date in a series under investigation at present in this laboratory.<sup>23</sup>

We do not intend to draw any conclusion from these data, but it appears from the few figures available that the vitamin A content of the liver in hemochromatosis is far below that in nondiabetic chronic disease, diabetes, acute atrophies and cirrhosis of the liver.

*Lipids in the Liver*—The various lipids in the liver were determined by the methods reported by Rubin, Present and Ralli,<sup>24</sup> of this laboratory. The results are given in table 2. The total lipid content of the liver (4.97 Gm per hundred grams of liver) in our case is between the values reported by Theis<sup>25</sup> (3.45 to 3.04 per cent) and those by Breusch

20 Davies, A. W. *Biochem J* **27** 1770, 1933.

21 Wolff, L. K. *Lancet* **2** 617, 1932.

22 Breusch, F., and Scalabrino, R. *Ztschr f ges exper Med* **94** 569, 1934.

23 Flaum, G., and Stueck, G. H. Jr. Unpublished data.

24 Rubin, S. H., Present, C., and Ralli, E. P. *J Biol Chem* **121** 19, 1937.

25 Theis, E. R. *J Biol Chem* **82** 327, 1929.

and Scalabrino<sup>22</sup> (5.16 to 6.43 Gm per hundred grams). The phospholipid-neutral fat ratio of approximately 1 is lower than that (1.5) reported by Theis. The value for lipid phosphorus (0.08 Gm per hundred grams of liver) is in the range reported by Breusch and Scalabrino (0.098 to 0.066 Gm per hundred grams). The values just reported are included in a study of the lipid content of normal and abnormal human livers being made in this laboratory at present.

*General Comment*—The case described illustrates the four classic clinical features of the disease, namely, enlargement of the liver, cutaneous pigmentation, diabetes mellitus and loss of secondary hair. It is well known that patients may survive the pigmentation and enlargement of the liver for many years, but that with the onset of diabetes the prognosis is limited. In this instance we have evidence of the presence of pigmentation and enlargement of the liver at least seven years prior to the final admission. During this period there were no symptoms save one gastrointestinal upset (possibly unrelated) in 1929. If we assume that the onset of diabetes occurred at the time of symptoms of that disease, the patient survived this by only three months.

"Resistance" to insulin has been reported in cases of hemochromatosis.<sup>26</sup> A tendency to hypoglycemia has also been reported.<sup>27</sup> Our patient demonstrated a good response to insulin therapy on a high carbohydrate diet, both while he had ketosis and while he was ambulatory, as evidenced by a progressively lower insulin requirement while he was on a diet of constant composition.

Reports of liver function tests in cases of hemochromatosis are few in the literature. In our case there was a normal result in the bromsulphalein excretion test (5 per cent retention) early in the patient's period of hospitalization. Seven weeks later there was 100 per cent retention of the dye. The rapidly progressing hepatic dysfunction, together with the onset of diabetes, the appearance of ascites and a mode of death similar to the "liver failure" seen in the terminal stage of cirrhosis of the liver, constituted the terminal episode of a long-standing disease. It has been suggested by some observers<sup>28</sup> that ascites is more common in hemochromatosis after insulin therapy. A more likely conception is that the diabetes is the forerunner of ascites in rapidly progressing dysfunction of the liver.

That there is no "characteristic electrocardiogram" is not difficult to understand. The extent and location of the pigmentation and fibrosis

26 Miller, H. A., and Hemmark, J. J. *Minnesota Med* **14** 260, 1931. Root, H. F. *New England J Med* **201** 201, 1929.

27 Stetson, R. P., and Peters, J. P. *Carbohydrate Metabolism in a Case of Hemochromatosis*, *Arch Int Med* **50** 226 (Aug.) 1932.

28 Bingel, A. *Munchen med Wchnschr* **79** 1750, 1932.

of the myocardium would determine any change in the electrocardiogram, particularly if the process involved any of the ramifications of the conduction system. Pigmentation alone may not alter the electrocardiogram.

Sheldon has pointed to the possible correlation of the clinical findings of loss of hair and impotence with the postmortem observations in the endocrine glands. Changes are more striking in the anterior lobe of the pituitary gland and the cortex of the adrenals, both of which structures are known to be associated with the clinical features mentioned. In our case a history of impotence was not obtained, but the absence of secondary hair has been pointed out. There was marked pigmentation of the outer layer of the adrenal cortex, unfortunately, the pituitary gland was not saved for microscopic section.

Various toxic agents have been suggested as the etiologic factor in this disease. In 1921 Mallory, Parker and Nye<sup>12</sup> offered chronic copper poisoning as a likely one. This view was also expressed by Hall and Butt,<sup>29</sup> but was denied by Flinn and Von Glahn<sup>30</sup> and by Polson.<sup>31</sup> Alcohol, acting alone or with copper as a contaminant, has been suggested as another possible agent. In our case there was a history of alcoholism over a period of years and of occupational exposure to zinc, lead and arsenic during twelve years the patient spent as a paint mixer. Lead was found in the liver in a concentration of 0.12 mg per 500 Gm. Arsenic was absent, the copper and the iron content have been reported

#### SUMMARY

We have described a case of hemochromatosis in a 39 year old white man with enlargement of the liver, cutaneous pigmentation, diabetes mellitus and absence of secondary hair. The course of the disease over eleven weeks is presented, including diabetic ketosis on admission, the initial appearance of ascites and a mode of death typical of the "liver failure" seen in cirrhosis of the liver. The postmortem observations are recorded, together with an analysis of the liver for lipids, heavy metals and certain pigment reactions.

Dr Douglas Symmers, director of the pathologic laboratories, Bellevue Hospital, permitted us to use the protocol of the necropsy summarized in this report.

29 Hall, E. M., and Butt, E. M. Experimental Pigment Cirrhosis Due to Copper Poisoning. Its Relation to Hemochromatosis, *Arch Path* 6:1 (July) 1928.

30 Flinn, F. B., and Von Glahn, W. C. *J Exper Med* 49:5, 1929.

31 Polson, C. J. *Brit J Exper Path* 10:241, 1929.

# RATE OF REMOVAL OF THORIUM DIOXIDE FROM THE BLOOD STREAM

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In order to obtain data concerning the function of the cells which clear the blood of large particles, the velocity of removal from this fluid of colloidal thorium after intravenous injection was determined under normal conditions for dogs subsequently subjected to procedures designed to alter the activity of these cells

There have been several previous studies of reticuloendothelial activity, determining the rate of removal of injected large molecular masses in the form of bacteria,<sup>1</sup> colloidal metals (silver,<sup>2</sup> manganese<sup>3</sup> and saccharated ferric oxide<sup>4</sup>), quartz,<sup>5</sup> carbon,<sup>21</sup> egg yolk,<sup>6</sup> egg albumin,<sup>7</sup> bilirubin<sup>8</sup> and various dyes (congo red,<sup>9</sup> brilliant vital red,<sup>10</sup> trypan blue,<sup>11</sup> bromsulphalein<sup>12</sup> and a series of acid and basic dyes<sup>13</sup>). Difficulties follow the use of all these substances which do not attend the use of thorium. All the dye studies have been complicated by excretion from the organism during the test period, so that the rate of removal from the blood represented in part ingestion by macrophages and in part elimination from the body. The injected neutral fat has been in the

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form of egg yolk, to which the animals have become allergic, limiting the number of observations. The methods of identification have been unsatisfactory for the determination of quartz and carbon. Difficulties have been experienced with the colloidal metals either in the preparation of a satisfactory suspension, as in the case of manganese dioxide, or through toxicity, in the case of silver and iron, limiting the amount that can be injected. The bacterial removal was determined by colony counts.

Colloidal thorium dioxide seemed to be more satisfactory than any substance previously used. It consists of large electronegative molecules, submicroscopic in size and insoluble in aqueous solutions, which are stored in the cells of the so-called reticuloendothelial system. It is eliminated in the merest traces from the organism<sup>14</sup>. Further, large amounts can be injected intravenously without immediate toxic effect, and satisfactory methods exist for the chemical estimation of thorium. An objection to its use lies in its radioactivity, toxic changes being produced after many months, but no immediate toxic effects were detected from the doses used.

#### METHOD

Colloidal thorium dioxide<sup>15</sup> was injected intravenously in doses of 9 to 12 cc (2.25 to 3 Gm of thorium dioxide) into 19 normal dogs, weighing 8 to 20 Kg. Each dog was always given the same amount of thorium, the maximum amount was 38.5 Gm of thorium dioxide over three months. After the injection 7 cc of blood was withdrawn at frequent intervals for three hours in a syringe moistened with saturated potassium oxalate and was centrifuged immediately for ten minutes at high speed in a tube to which 1 drop of this anticoagulant had been added. The amount of thorium was determined by a micromethod, and a curve was constructed with respect to the time interval.

The chemical method of estimating the amount of thorium was a slight modification of a standard method<sup>16</sup>. All analyses were made in triplicate. One or two cubic centimeters of plasma was digested with 2 cc of concentrated sulfuric acid and fuming nitric acid over a microburner until the carbon had been destroyed. After the solution had been cooled in an ice bath, about 40 Gm of pulverized ice was added to form the octahydrate of thorium sulfate. The solution was then transferred to a large centrifuge tube, made alkaline to phenol red with concentrated ammonium hydroxide and allowed to stand for thirty minutes. The precipitate of thorium was then centrifuged for ten minutes, the supernatant fluid discarded and the precipitate washed with water and centrifuged again. The precipitate was then dissolved in 1 or 2 drops of concentrated hydrochloric acid and transferred to a 15 cc narrow-tipped centrifuge tube, 1 cc of 10 per cent oxalic acid was added and the mixture placed in the ice box over night. The

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14 Angermann, M., and Overhof, K. *Ztschr f d ges exper Med* **94** 121, 1934.

15 The preparation used was thorotrast, manufactured by the Heyden Chemical Corporation, 50 Union Square, New York, and contained 24 to 26 per cent thorium dioxide by volume.

16 Schoeller, W. R., and Powell, A. R. *The Analysis of Minerals and Ores of the Rarer Elements*, Philadelphia, J. B. Lippincott Company, 1919, p. 104.

thorium oxalate precipitate was then washed three times with water, care being taken in decanting the supernatant fluid, and then titrated at 90 C with hundredth-normal potassium permanganate. During the chemical procedure, traces of iron and calcium phosphate are carried over with the thorium, and it is necessary to determine the oxalate equivalent by making a blank determination of the plasma content before the injection of thorium dioxide, this equivalent is deducted from the total amount of permanganate used. The blank value varied from 0.07 to 0.13 cc of hundredth-normal potassium permanganate. The calculation, then, is: One cubic centimeter of hundredth-normal potassium permanganate equals 0.66 mg of thorium dioxide. The error of the method is less than 5 per cent.

The rate of removal of thorium was determined for dogs anesthetized with ether and with intravenously injected pentobarbital sodium (0.025 Gm per kilogram). The surgical procedures were carried out with the animals under ether anesthesia and with an aseptic technic.

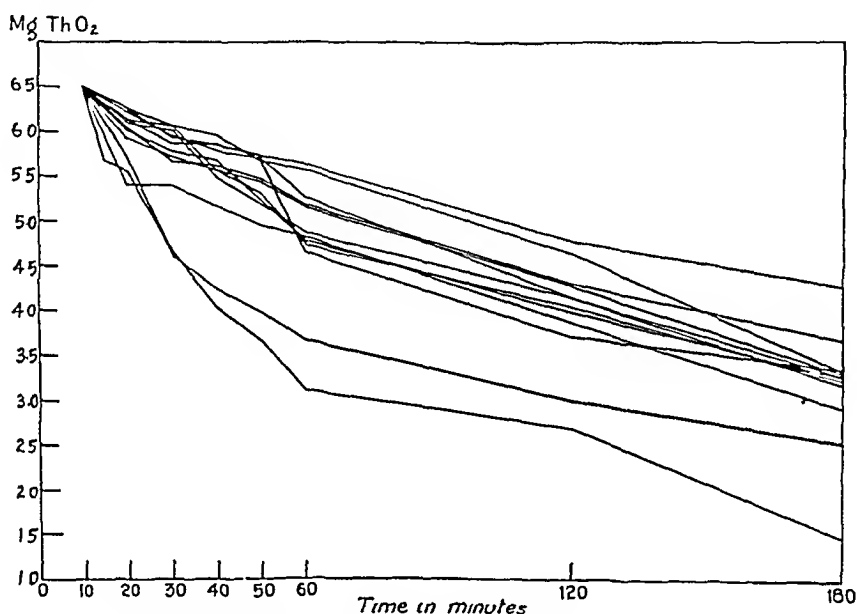


Chart 1—Curves obtained during a three hour period following injection of thorium dioxide into normal dogs. Values at ten minutes after injection were placed at the same point so that the slope of the curve could be composed.

## RESULTS

*Normal Dogs*—Two to six curves were obtained for each dog. The curves for 14 dogs showed a similar general slope (chart 1), but in 2 cases the colloid was removed at a faster rate than in the others. The type of curve remained the same for each normal dog for at least two months. The rate of removal was always fastest within twenty minutes after the injection and then became slower. For 4 dogs a flat region in the curve was detected between twenty and forty minutes after the injection. Thorium was found to disappear completely from the blood between ten and twelve hours after the injection. While the slope of the curve remained the same for any normal dog, the absolute values

of thorium differed slightly, depending probably on the differences in the volume of the blood from day to day

*Anesthesia*—No changes were detected in the curves of thorium removal after ether or pentobarbital sodium anesthesia (chart 2) No attempt was made to keep the body temperature at a normal level, and a decrease in the temperature of 2 to 6 degrees (F) in the rectum was uniformly found in one hour in dogs anesthetized at room temperature

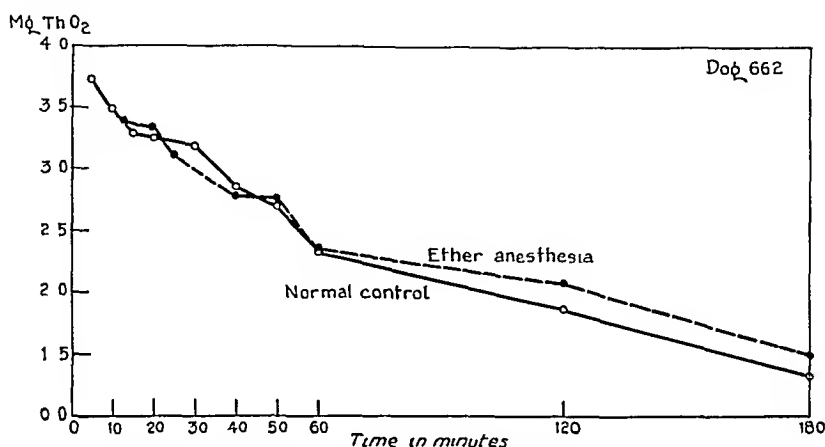


Chart 2—Curves obtained for a dog under normal conditions during and following ether anesthesia for one hour

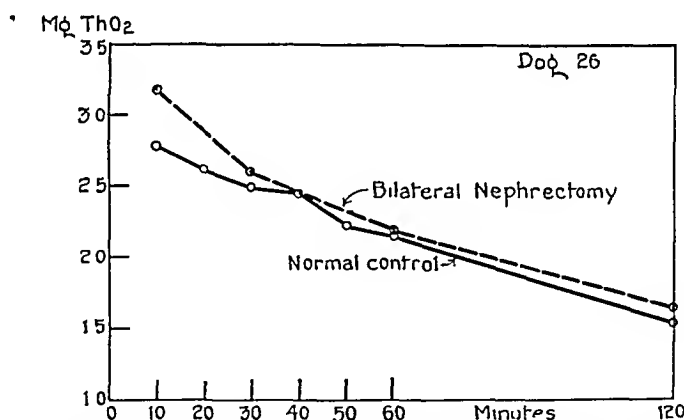


Chart 3—Curves obtained in a control period and three days following bilateral nephrectomy

(20 to 25 C) A decrease in body temperature thus did not affect the velocity of removal with the animal under anesthesia

*Bilateral Nephrectomy*—No changes occurred in the curve (chart 3) even four days after the operation, when there was severe uremia

*Splenectomy*—This operation, carried out on 4 dogs, increased the removal slightly in each case In 3 cases the curve had returned to normal in forty-eight hours and in 1 case (chart 4) six days after operation

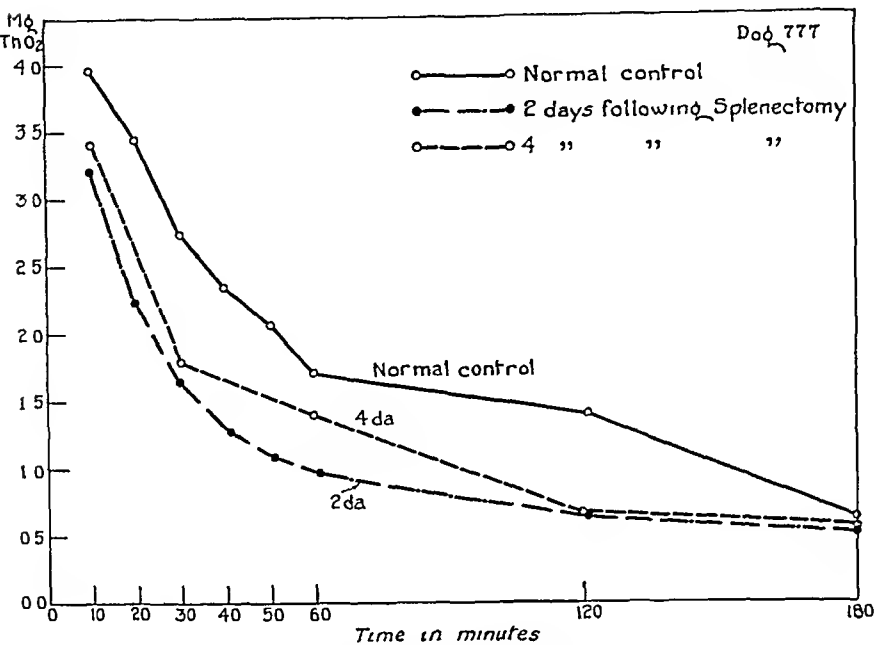


Chart 4—Normal and postsplenectomy curves

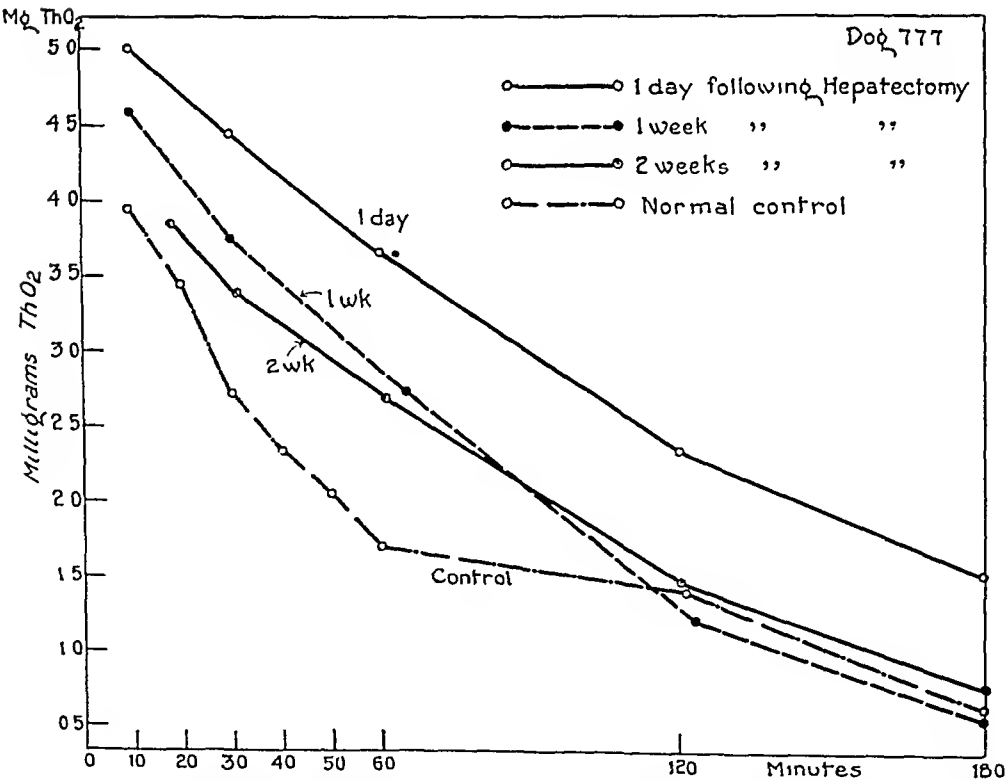


Chart 5—Curves obtained during a control period and after surgical removal of 34 per cent of the liver



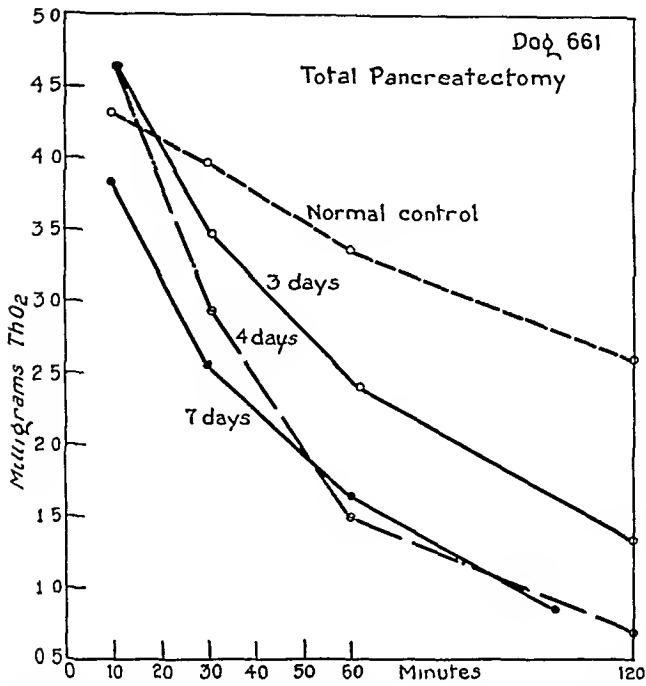


Chart 6—Normal and postpancreatectomy curves showing the removal of thorium dioxide from the blood

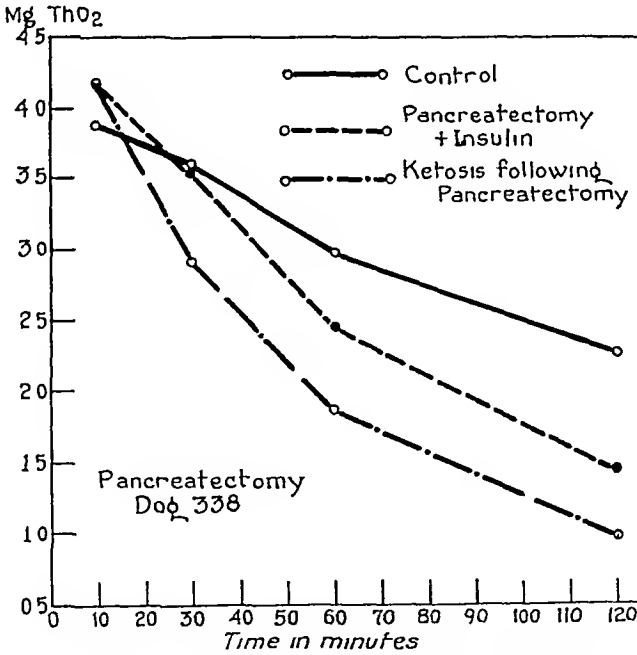


Chart 7—A normal control curve and postpancreatectomy curves with and without control of ketosis and glycosuria with insulin

*Partial Hepatectomy*—From 4 dogs the largest, left lobe of the liver was removed, and from 2 of these a large right lobe was also removed. By comparing the weight of the liver removed to the weight of the liver remaining at autopsy, 19.8 to 36 per cent of the liver was removed. Thorium curves were plotted one, two, four, seven and fourteen days after the operation. In all cases the rate of removal was slowed on the first and second days. For 2 dogs the curve had returned to normal after seven days and for all dogs fourteen days after partial hepatectomy (chart 5).

*Total Pancreatectomy*—The pancreas was removed from 5 dogs. Insulin was not given for eight days. Four dogs died between the fifth and the seventh day following operation, 1 dog was studied for forty-two days. At least two thorium curves were obtained after operation for each dog. In all cases an increased rate of removal occurred (charts 6 and 7). The diabetes was controlled in 1 dog by means of injections of protamine insulin, and curves were obtained during alternating periods of control of glycosuria and ketosis. During the periods of ketosis the rate of removal was always faster than during the control periods, although no final opinion can be drawn from a single case. The total lipid content of the blood was found to be increased 0.2 to 0.45 Gm over that for the control period, at a time when increased removal was occurring.

#### COMMENT

The most interesting findings derived from these data seem to be the great functional reserve of the reticuloendothelial system and the difficulty of greatly interfering with the capacity of its cells. The absence of an effect two days or more after splenectomy is in agreement with the findings of Klein and Levinson<sup>12a</sup> and of Mills and Dragstedt,<sup>12b</sup> who found slight or no changes in the rate of removal of bromsulphalein from splenectomized dogs, although a recognizable fraction of this "system" had been removed. Removal of about one quarter of the liver, however, did slow the removal rate for a few days.

It is well known that in dogs that have undergone total pancreatectomy, purulent conjunctivitis and wound and other infections are more likely to develop than in nondiabetic dogs. The finding that particulate matter is removed at a faster rate from diabetic dogs than from normal animals is of interest in connection with this decreased resistance to infection and indicates that the ability of the macrophages to ingest particles is not the cause of the disturbance.

#### SUMMARY AND CONCLUSIONS

The curves for the removal from the blood of injected colloidal thorium dioxide were similar for 14 dogs, but in 2 cases the velocity

was appreciably faster. This colloid is removed fastest during the first twenty minutes after injection, then at a slower rate, until it disappears from the blood between ten and twelve hours, with the doses used. The rate of disappearance of thorium was not significantly affected by ether or pentobarbital sodium anesthesia, by bilateral nephrectomy or by splenectomy. The rate slowed after the removal of about one quarter of the liver and was increased during the diabetes following pancreatectomy.

The evidence shows that the decreased resistance to infection of diabetic dogs is not caused by an inability of macrophages to ingest large particles, such as bacteria.

Dr Lillian Eichelberger and Dr Paul B. Donovan gave advice and assisted in this study.

# INTUBATION OF THE HUMAN SMALL INTESTINE

## XII THE TREATMENT OF INTESTINAL OBSTRUCTION AND A PROCEDURE FOR IDENTIFYING THE LESION

W OSLER ABBOTT, M D

PHILADELPHIA

Intestinal intubation<sup>1</sup> may now be regarded as an established clinical procedure. It has been employed in more than five hundred instances in the clinic of the Hospital of the University of Pennsylvania and to a less extent in a number of other institutions in this country and abroad. The technic is time consuming and may be difficult even for the experienced worker. The results obtained in the management of intestinal obstruction alone, however, seem to justify its inclusion among the procedures available in all large general hospitals. The employment of the method in 16 cases of acute obstruction has previously been described (Abbott and Johnston<sup>2</sup>), but further experience has indicated in more detail the various ways in which the method is therapeutically and diagnostically helpful in such cases. It may be utilized advantageously throughout the acute phases of the patient's illness and its beneficial effects include, in chronologic order, the possibilities (*a*) of emptying the intestine and restoring peristalsis, (*b*) of supplying promptly the data needed in the adjustment of the fluid and electrolyte balances of the body, (*c*) of relieving the obstruction itself, (*d*) of identifying the location and nature of the lesion, (*e*) of simplifying the technic of any required surgical procedure, (*f*) of protecting the suture line after operation and (*g*) of converting an emergency into an elective surgical procedure.

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Aided by a grant from the Committee on Scientific Research of the American Medical Association

From the Gastrointestinal Section (Kinsey-Thomas Foundation) of the Medical Clinic, Hospital of the University of Pennsylvania

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1 Miller, T G, and Abbott, W O. Intestinal Intubation. A Practical Technique, *Am J M Sc* **187** 595-599 (May) 1934

2 Abbott, W O, and Johnston, C' G. Intubation Studies of the Human Small Intestine. X A Non-Surgical Method of Treating, Localizing and Diagnosing the Nature of Obstructive Lesions, *Surg, Gynec & Obst* **66** 691-706 (April) 1938

## TECHNIC

The technic of intubation of the obstructed intestine is the same as that already described for the normal<sup>1</sup> and for the obstructed bowel.<sup>2</sup> It may be carried out with any apparatus which includes (1) a rubber tube for the aspiration of intestinal contents, (2) a thin rubber balloon at the end of the tube for engaging peristalsis and (3) a fine rubber tube for inflating the balloon. Either a tube with a double lumen or a large and a small tube tied together will suffice (fig. 1). An opening, for the aspiration of contents, is often placed distal to the balloon, thus facilitating decompression ahead of the instrument. Preferably, because the tube at times must be kept in place for several days, the apparatus should be introduced through the nose. The balloon must never be inflated until it has entered the duodenum, for a full balloon will not leave the stomach. In the absence of a fluoroscope with which to identify the location of the tube, since gastric and duodenal contents in the obstructed intestine are often indistinguishable, the presence of the tip of the tube in the duodenum may be determined by the feel of the syringe plunger as the initial 10 cc. of air is injected into the balloon, the gentle, rhythmic resistance of the duodenum contrasting sharply with the lack of all sense of resistance when the balloon lies in the stomach. If the tip has not advanced sufficiently, this inflation may cause it to be regurgitated back through the pylorus, but if it is well placed, the balloon will advance rapidly, and the patient will perceive that the tube is slipping more easily down his throat as the intestine starts propelling the balloon.

THE ADVANTAGES OF INTUBATION AS AN ADJUNCT IN THE  
TREATMENT OF INTESTINAL OBSTRUCTION

(a) *The Intestine Can Be Decompressed and Peristalsis Restored* —

This fact has been repeatedly manifested. It has been shown (Abbott, Zetzel and Glenn<sup>3</sup>) that peristalsis is first rendered more effective and then abolished by progressive distention and that in the presence of mechanical obstruction a zone of absent peristalsis, preceded by a zone of hyperperistalsis, extends progressively orad from the point of blockage. Until death of the muscularis results, this process is reversible. Thus a patient who has had an obstruction for a long time and who presents great distention of the abdomen, with no audible peristalsis, or one who has shown paralytic ileus from the start may undergo intubation successfully because, as the stomach, the duodenum and the subsequent sections of small bowel are deflated, each in turn regains its peristaltic activity and forces the balloon onward. As this takes place the patient experiences striking relief of pain and abatement of his shocklike symptoms, the normal motor function of the intestine being at the same time restored.

Reverse peristalsis distal to the duodenum has not as yet been observed in any case, the orad flow of intestinal contents resulting from

3 Abbott, W. O., Zetzel, L., and Glenn, P. M. Observations on the Motor Activity of the Obstructed Small Intestine Made During the Course of Treatment by Intubation, *Am. J. M. Sc.* 195 279-280 (Feb.) 1938.

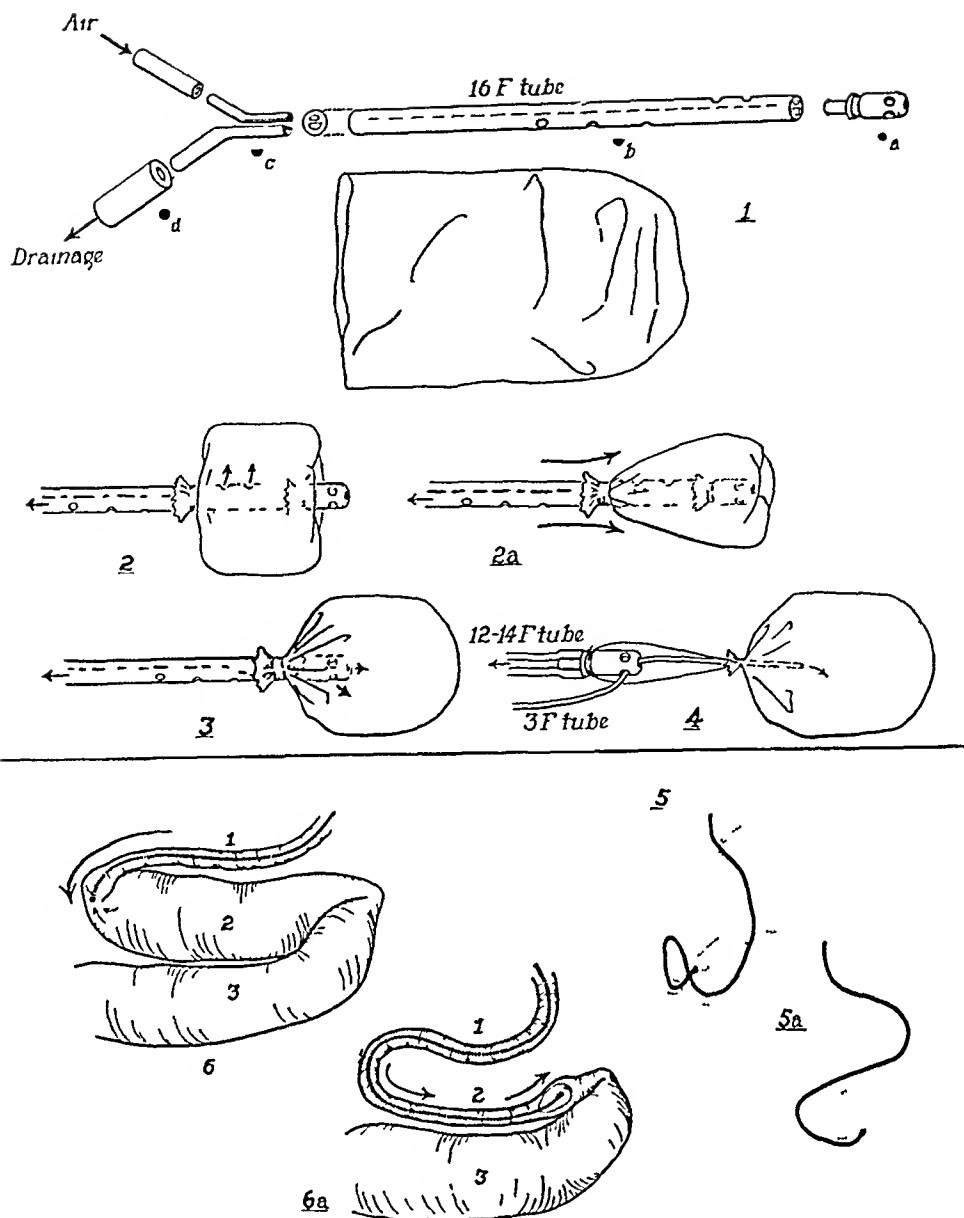


Fig 1—Technic of Intubation 1, the component parts of a tube for the small intestine, *a*, the aspirating tip, size 16 F, *b*, double-lumened tube with perforations from the small lumen for inflation of the balloon and into the large lumen for aspiration of intestinal contents, *c*, metal connections, *d*, round rubber tubing connecting the apparatus to aspirating bottles or to a syringe for the injection of air (the rubber balloon is cut to the correct size before being tied on the tube) It is of great importance in assembling a tube to safeguard against blockage by seeing that the diameter of the lumen of every part from tip to bottle increases progressively 2, the tube assembled for aspiration both ahead of and behind the balloon In 2*a* is shown the importance of a loose balloon that can sag forward, temporarily covering the tip as it advances 3, the tip is mounted on the small lumen so that the balloon precedes the tube, an assembly that is particularly useful in the presence of multiple adhesions 4, the balloon on a separate tube draws a single-lumened aspirating tube after it, a device used chiefly in cases of multiple partial obstructions 5 and 5*a*, the fluoroscopic appearance of tubes at the point in the duodenum at which the balloon may safely be inflated without fear of its being regurgitated back into the stomach 6 and 6*a*, the way in which a tube is believed to empty the intestine, segment by segment, deflating it, allowing the blood supply to return and then being advanced to the next point of angulation by the returning peristalsis

hypersecretion above the obstruction, as described by Herrin and Meek<sup>4</sup> while peristalsis, rendered incompetent by the dilatation of the intestine, behaves, as Brinton<sup>5</sup> described it, like a hollow piston in a cylinder without an outlet. It has frequently been contended that suppression of peristalsis is a toxic manifestation (which in some instances it may be), but the following case is an instance in which overwhelming toxemia failed to prevent the restoration of peristalsis after satisfactory decompression.

H. X., a woman of 41 years, was in good health until the abrupt onset of severe abdominal pain. Twenty-four hours later she was admitted to the service of L. D. Englerth, and at operation volvulus of the cecum and the terminal portion of the ileum was present. The loop of bowel was gangrenous and had ruptured, spilling feces throughout the peritoneal cavity. The stumps of the ileum and cecum were exteriorized, and the pelvis was drained. At first the abdominal symptoms were controlled by Wangenstein drainage, but six days after operation distention of the bowel suddenly became marked and her temperature rose sharply. On the seventh day, though the patient was critically ill and had no audible peristalsis, intubation was performed. She died of general peritonitis thirty-six hours later, but for the last twenty-four hours of life peristalsis was active, the abdomen was flat and feces were discharged through the stump of the ileum.

(b) *The Control of the Fluid and Electrolyte Content of the Body Is Facilitated*—On admission the patient with critical obstruction is likely to present a state of shock. The extremities are cold and blue, and the pulse is rapid and thready. The relief of pain that comes with intestinal decompression may improve the situation markedly, but the fundamental chemical imbalance, as a rule involving water, electrolytes and serum protein, must be corrected as rapidly and accurately as possible if the patient is to survive. The work of Hartwell and Hoguet,<sup>6</sup> of Haden and Orr<sup>7</sup> and of many others has shown the character of the deviations from normal to be expected, but the great practical difficulty in accurate replacement therapy has always depended, in the first place, on the delay in securing a report on the chemical examination of the blood and, in the second place, on the rapidity with which the state of the patient changes. In a word, successful maintenance of a patient with obstruction depends on a reasonably accurate estimation of his needs in terms of fluid, electrolytes and plasma protein almost from hour

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4 Herrin, R. C., and Meek, W. J. Distention as a Factor in Intestinal Obstruction, *Arch Int Med* **51** 152-168 (Jan.) 1933.

5 Brinton, W. Intestinal Obstruction, edited by T. Buzzard, London, John Churchill & Sons, 1867.

6 Hartwell, J. A., and Hoguet, J. P. Experimental Intestinal Obstruction in Dogs, with Especial Reference to the Cause of Death and the Treatment by Large Amounts of Normal Saline Solution, *J. A. M. A.* **59** 82-87 (July 13) 1912.

7 Haden, R. L., and Orr, T. G. Chemical Changes in the Blood of the Dog After Obstruction of the Duodenum, *J. Exper. Med.* **37** 365-375 (March) 1923.

to hour at the start. Intubation permits such determinations because it allows one to measure exactly the loss of fluid from the body into the intestine, otherwise impossible, and since the salt content of such fluid is approximately that of the blood plasma, one can, by making adjustments for the fluid taken by mouth, estimate roughly the amount of sodium chloride needed. The following cases indicate certain of these fluid and electrolyte relations.

S W, a man aged 75 years, was in good health until a sharp pain occurred in the right lower quadrant of the abdomen. Three days later, after much colicky pain and distention, he was admitted to the service of E L Eliason, and a ruptured appendix with a pericecal abscess was present at operation. By the second postoperative day the intestinal obstruction was the major problem. The patient was drowsy and somewhat dehydrated, the abdomen was distended, peristalsis was inaudible and vomiting was occurring intermittently. The chloride content of the plasma was 91 milliequivalents per liter. Intubation was performed, and the patient was given liquids by mouth as the tube went down the intestine. Though his condition seemed critical, he improved rapidly and on the fourth day after operation was alert and in good condition. On the fifth day he complained of pain in the chest. Fever rapidly developed, and death due to bronchopneumonia occurred on the sixth day after operation. Table 1 indicates the relative constancy of the sodium chloride concentration in the intestinal drainage in this case, in spite of the rather wide variations in the amount and in the route of the water and fluid received together with the large volume recovered by drainage.

In contrast is the case of E H, a woman of 53 years, admitted to the service of E L Eliason, who was operated on for annular carcinoma of the rectosigmoid flexure. The first stage of a Mikulicz operation was performed, followed in two days by the second stage. On the day following the latter procedure, marked distention set in, unrelieved by Wangensteen drainage. On the fifth day after the original operation, intubation of the jejunum was done. On the ninth day, her condition being greatly improved, the third stage of the operation was performed, the tube was withdrawn and uneventful convalescence followed.

Table 1 shows data on the intake and output of salt and fluid in 2 cases. From this it appears that within wide limits the concentration of salt in the drainage is unaffected by the salt content and the volume of fluid ingested. The observed range being so narrow, one can estimate closely the amount of sodium chloride lost in the drainage and can replace a comparable amount within a few hours. This is a real help in avoiding not only hypochloremia but also the possibility of hyperchloremia, with mucosal edema which might in turn increase the obstruction.

(c) *Relief of the Obstruction Is Obtained by Intubation*—Wangensteen<sup>8</sup> has pointed out that decompression of the stomach and duodenum will occasionally result in the relief of the obstruction itself. This is

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<sup>8</sup> Wangensteen, O H. *The Therapeutic Problem in Bowel Obstructions. A Physiological and Clinical Consideration*, Springfield, Ill., Charles C Thomas, Publisher, 1937.



TABLE 1—Clinical Data for Two Patients

Clinical Data			Intake			Intestinal Drainage							
Patient	Period of Obstruction, Days	Position of Tube	Time Interval		Fluid, Cc		Salt, Gm		Volume, Cc	Sodium Chloride, Gm	Rate of Flow, Cc/Hr	Concentration of Sodium Chloride, Gm per 100 Cc	
			Mouth	Vein	Total	Mouth	Vein	Total					
S W	2	Jejunum	2 00 p m	7 00 p m	1,045	1,000	2,045		9 0	9 0	370	0 54	
		Jejunum, low	7 00 p m	12 00 p m	780		780				370	0 37	
		Ileum, high	12 00 p m	6 00 a m	1,380		1,380				300	0 37	
J		Ileum	16 hours		3,205	1,000	4,205		9 0	9 0	343	0 43	
			6 00 a m	1 30 p m	1,435	1,000	2,435		9 0	9 0	223	0 32	
			1 30 p m	6 30 p m	1,090	833	1,923	1 0	6 1	7 1	283	0 37	
4		Ileum, low	6 30 p m	2 00 a m	2,050		2,050		9 3	9 3	246	0 50	
			2 00 a m	7 00 a m	1,000		1,000				220	0 38	
			25 hours		5,575	1,833	7,408	1 0	15 1	16 1	243	0 46	
5		Ileum, low	7 00 a m	1 30 p m	1,335	1,000	2,335	0 6	9 0	9 6	261	0 55	
			1 30 p m	7 00 p m	1,380	1,300	2,680	6 5	24 0	27 3	273	0 79	
			7 00 p m	6 00 a m	2,640	1,300	3,940		10 5	10 5	168	0 54	
6		Ileum, low	23 hours		5,415	3,600	9,015	7 1	43 5	52 6	219	0 62	
			6 00 a m	12 00 a m	1,810	1,000	2,810	0 6	9 0	9 6	300	0 46	
			12 00 a m	6 00 p m	600	1,000	1,600		7 8	7 8	221	0 49	
7		Ileum, low	6 00 p m	6 00 a m	1,830	1,300	2,330		13 5	13 5	154	0 36	
			24 hours		4,210	3,500	6,740	0 6	30 3	30 9	235	0 50	
			6 00 a m - 2 00 p m		1,090	1,000	2,090	1 0	9 0	10 0	222	0 46	
H	5	Stomach to jejunum	Died three hours later of bronchopneumonia, last specimen lost										
			7 00 a m	7 00 p m	540	1,000	1,540	0 2	9 0	9 2	25	35	
			7 00 p m	6 00 a m	840	1,000	1,840	1 0	9 0	10 0	22	45	
6		Ileum	23 hours		1,380	2,000	3,380	1 2	18 0	19 2	40		
			6 00 a m	6 00 p m	470	1,000	1,470	0 5	6 0	6 5	157	0 53	
			6 00 p m	7 00 a m	310	1,000	1,310	0 9	9 0	9 9	67	0 79	
7		Ileum	25 hours		780	2,000	2,780	1 4	15 0	16 4	112	0 67	
			7 00 a m - 7 00 p m		1,800	2,500	4,300	0 5	22 5	23 0	141	0 66	
			7 00 p m	7 00 a m	880	2,000	2,880	1 5	9 0	10 5	69	0 66	
8		Ileum	24 hours		2,680	4,500	7,180	2 0	31 5	33 5	105	0 66	
			7 00 a m	7 00 p m	1,620	3,925	5,545	0 7	35 1	35 8	104	0 47	
			7 00 p m	7 00 a m	1,480	1,656	3,130		15 3	15 3	104	0 73	
			21 hours		3 100	5 575	8,675	0 7	50 4	16 5	104	0 60	
Intestinal activity returned, tube was withdrawn, convalescence was uneventful													

seen even more often after aspiration of the contents of the entire small intestine above a lesion. In a patient with temporary obstruction due to a local inflammatory reaction, the condition will sometimes subside if he can be kept alive long enough. When relief occurs, it is presumably the result of collapsing the intestine and of diverting the intestinal current, thus promoting free movement of the coils in the abdomen and subsidence of local inflammatory edema. In some instances it is advisable subsequently to operate and to remove the abnormal structure, but in many instances the primary factor is a multiplicity of operations in the past. Even though another episode of obstruction may occur in a day or a year, it is desirable, when possible, to avoid the trauma of another laparotomy, as illustrated by the following case.

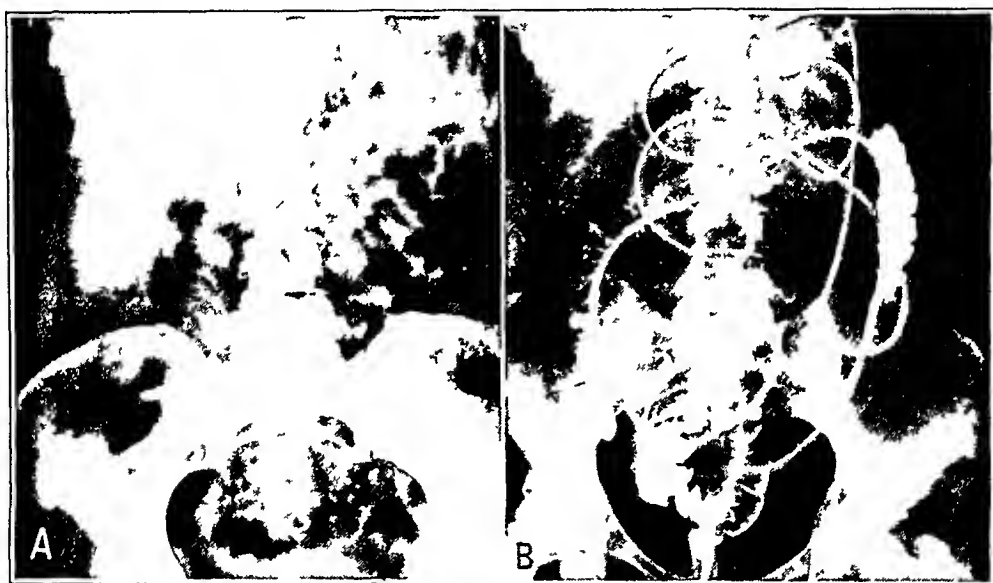


Fig 2—Relief of an obstruction caused by postoperative adhesions. V I, a patient aged 47, had been obstructed for six days. *A*, showing the distention of the abdomen on entry. The intestine being largely distended with fluid, only small collections of gas can be seen in the small intestine. *B*, the balloon has been expelled through the rectum, having passed through the entire alimentary canal.

V I, a woman of 47 years, had undergone a pelvic operation ten years earlier which left her with a tendency to constipation and the passage of flattened stools. Thinking that she was again constipated, she allowed four days to pass without a stool, but by the sixth day colicky abdominal pain and increasing distention led to her admission to the service of I S Ravdin. Although once or twice the passage of a drachm (4 Gm) of feces occurred, she presented clinical signs of mechanical obstruction and roentgenographic evidence of gas in the small intestine (fig 2). A tube was passed, and it advanced until the balloon lay in the ascending colon. The distention was relieved, and peristalsis was again normal. A barium sulfate enema was given at this time, and when the enema fluid was expelled, the balloon and a foot (30 cm) of tube were passed by rectum. Subsequently, though the acute obstruction was relieved, an operation was necessary to sever adhesions about the rectosigmoid flexure.

(d) *Roentgenographic Study of the Lesion Is Possible*—There are few who have the temerity to give a barium sulfate meal to a patient with acute obstruction, yet 50 or 100 cc of a dilute suspension of barium sulfate can safely be injected by tube (a) because it can be withdrawn again if the obstruction is complete and (b) because in a mechanically obstructed intestine, since the balloon goes actually to the obstruction, much can be learned from a minimal amount of opaque medium. This may be exemplified by the following case.

F D, a man of 36 years, had been ill for nine years, the diagnoses being tuberculous enteritis, regional ileitis, appendicitis and ulcerative colitis. Five abdominal operations had been performed during that period. He was admitted to the service of I S Ravdin after seven days of partial obstruction and after three days of complete obstruction. Distention was marked, fecal vomiting was incessant and each bout of retching ended in a tetanic spasm. The cold, blue extremities and rapid, thready pulse indicated a marked degree of shock (fig 3). A tube was at once placed in his stomach. Twelve hours later it had started down the small intestine. The fluid output approximated 6 liters a day for the first forty-eight hours and was balanced by fluids given intravenously, including blood and the required electrolytes. In thirty-six hours he was comfortable and sitting up in bed. On the third day of the patient's hospitalization the tip of the tube was observed fluoroscopically to lie in the right lower quadrant of the abdomen. A thin suspension of barium sulfate, totaling 50 cc, was injected, and films were exposed. From this study it was determined that excision of the right side of the colon, with an ileocolostomy opening to the mid portion of the transverse colon, had been done previously. An intrinsic constricting lesion of the terminal 6 inches (15 cm) of ileum was producing the obstruction, and although adhesions were present, it was felt that the lower portion of the ileum was free enough to permit a new ileocolostomy. This was carried out. The diseased tissue, which proved to be due to a recurrence of regional ileitis, was excised, and a satisfactory convalescence resulted, the tube being withdrawn on the third post-operative day (fig 4).

(e) *The Surgical Technic Is Simplified*—This is obviously true when one considers the difficulty of operating on a patient with thin-walled, distended intestines which are constantly threatening to extrude from the wound, in contrast to operating on a patient who arrives in the operating room with a flat abdomen and empty intestines, but even when preoperative decompression is incomplete because of multiple obstructions, the technic is still simplified, because by manipulating the tube at operation, the surgeon may be able to place its tip in one obstructed area after another until complete decompression is accomplished.

A H, a man of 63 years, was well until abdominal pain with constipation developed. During the first twenty-four hours the pain increased, and he took laxatives. After five days without a bowel movement, he was admitted to the service of I S Ravdin, with clinical signs of mechanical intestinal obstruction. The tube passed down the small intestine, but incomplete relief of distention resulted (fig 5). At operation on the fifth day following hospitalization, two

long-distended loops of intestine bulged from the wound. Three bands of adhesions were present, the first having stopped the tube. With the balloon deflated, the surgeon passed the tip of the tube under the first and then the second adhesion, the loops being emptied by means of a syringe applied to the proximal end of the tube. With the collapse of the distended intestine, the dissection of the adhesions and the replacement of the loops in the abdomen were greatly facilitated. Convalescence was uneventful.

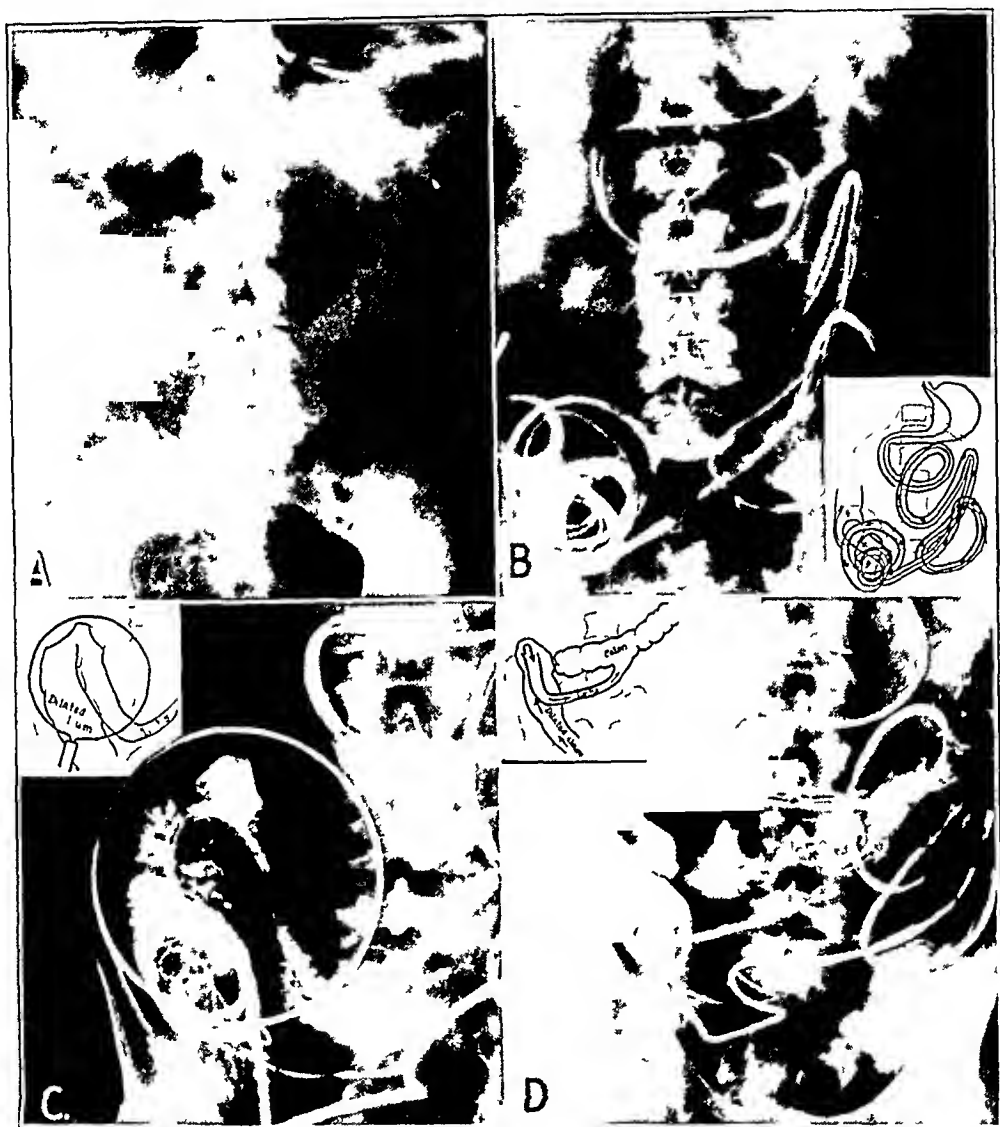


Fig 3—The injection of barium sulfate for diagnostic purposes. F. D., aged 36, had had partial obstruction for seven days and had had complete obstruction for three days due to recurrence of regional ileitis. *A*, showing distention of the small intestine with gas and fluid. The tube is entering the stomach. *B*, the tip lies in the right lower quadrant of the abdomen, with the tube coiled behind it in the dilated ileum. *C*, after the injection of 50 cc of a thin barium suspension and the application of pressure. The adhesions, pinning out the ileum, are apparent, together with the abrupt transition from dilated to constricted intestine. The tube, with the balloon deflated, has entered the constricted segment. *D*, barium has entered the colon, indicating (*a*) the site of the old ileocolostomy, (*b*) the length of the segment of ileum in which the ileitis has recurred and (*c*) the stump of transverse colon, demonstrating that the ascending colon had been excised.

(g) *Protection of the Suture Lines Results*—A tube in the intestine protects the suture line of an anastomosis from internal pressure. Frequently in cases of long-standing partial obstruction, as in acute complete obstruction, the intestine above the blockage is thin as paper, and the danger of leakage through the suture line, if resection is attempted, is far greater than after operations on more normal tissue.

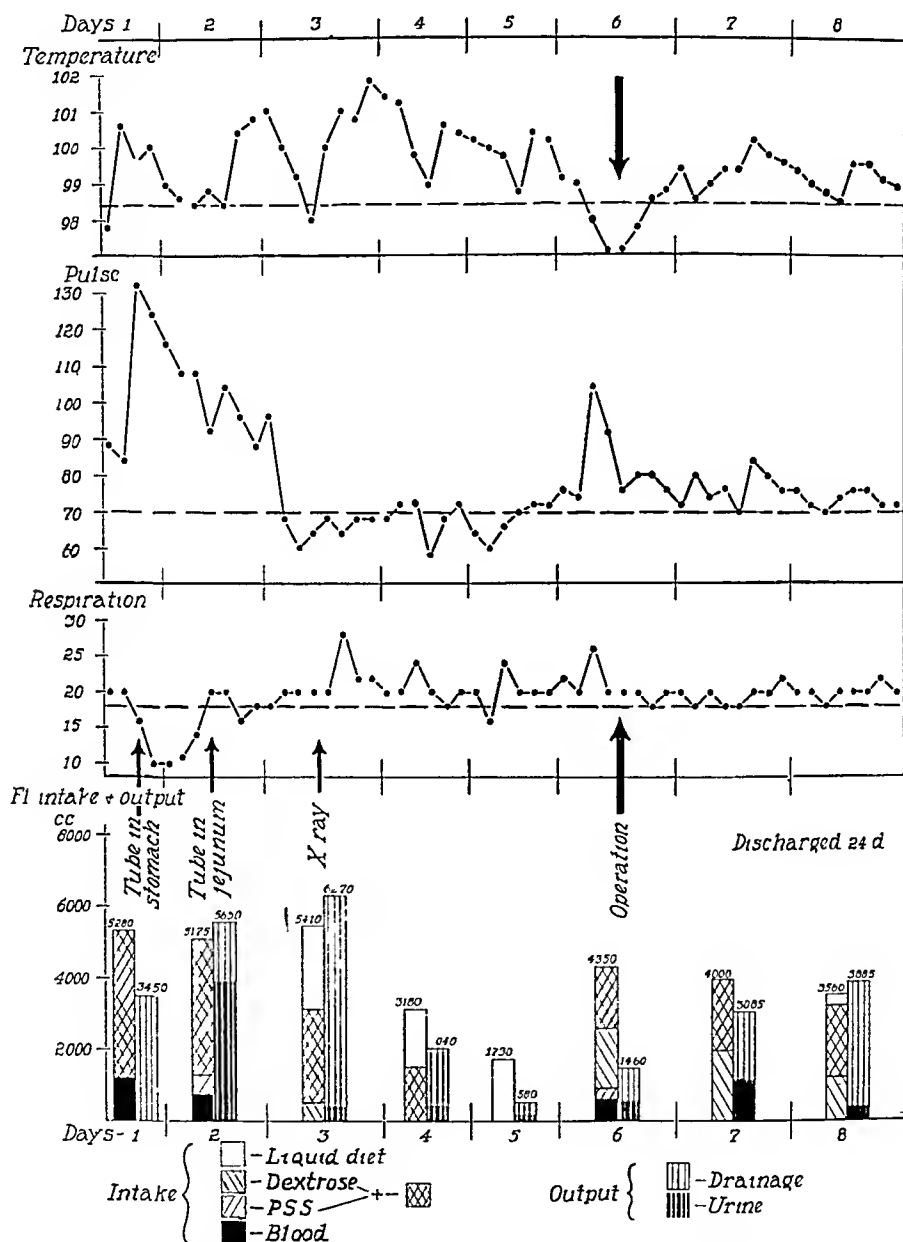


Fig 4—Acute intestinal obstruction F D, aged 36, had recurrent regional ileitis. He was admitted to the hospital seven days after the first attack of colic and three days after obstruction became complete. The temperature, pulse rate and respiration rate during treatment by means of intubation, roentgenographic studies, and finally resection of the diseased area, with the construction of a new ileocolostomy opening, are shown.

If there is a tube in the intestine above the point of operation during the early part of convalescence, it is possible to keep this part of the intestine empty, even though small amounts of fluid and food are taken by mouth from the day of operation. This was exemplified in the following case:

S. B., a man of 20 years, had been admitted to the service of I. S. Ravdin thirteen times in two years for the relief of regional ileitis and its complications. On his last entry he weighed only 70 pounds (31.8 Kg.) and had six fecal fistulas to different points on the abdominal wall and signs and symptoms of chronic intestinal obstruction. Previously appendectomy and ileocolostomy at the mid-portion of the transverse colon had been done. The terminal portion of the ileum and the cecum, however, had been left in place. Intubation was requested in an effort to locate the point of obstruction and the points of origin of the fistulous tracts. The tube was passed as far as it would go. Barium sulfate was injected into



Fig. 5—Incomplete decompression in the presence of multiple obstructions. *A*, a roentgenogram taken on entry, showing gastric dilatation and a collection of gas in the small intestine. *B*, after intubation and the injection of barium sulfate the opaque material can be seen to have entered a distended segment of intestine distal to the tip of the tube (arrow).

the terminal portion of the ileum and by catheter into the fistulas, while small amounts of barium were given in an enema. It became apparent that the cecum, ascending colon and half the transverse colon had contracted to form a fibrous pouch, about 15 cm. in length, in the right lower quadrant of the abdomen into which all the fistulas led (fig. 6). From this scarred area, fairly normal colon passed diagonally upward to the splenic flexure, while in the area of the ileocolostomy the intestine was markedly obstructed by bands of scar tissue, thus producing huge dilatation of the lower portion of the ileum. By manipulation of the tube it was determined that these coils were freely movable and that a new ileocolostomy was practicable. This was done. The colon and terminal portion of

the ileum were transected, and the ends toward the diseased area were turned in and oversewed, while the dilated end of the ileum was anastomosed to the left side of the transverse colon. The danger of operating on such an ill patient was appreciated, especially in view of the fact that the fecal fistulas were constantly contaminating the abdominal wall, but the chief concern was for the ileocolostomy anastomosis, because the terminal portion of the ileum was almost as thin as paper. The balloon was therefore deflated and then drawn back to a point well above the site of operation. Suction was maintained for three days after operation, and successful convalescence resulted (fig 7).

(h) *Operation Is Delayed*—Variable as are the enumerated advantages of intubation, there is still one of major and outstanding importance. The passage of a tube to the point of obstruction at once converts

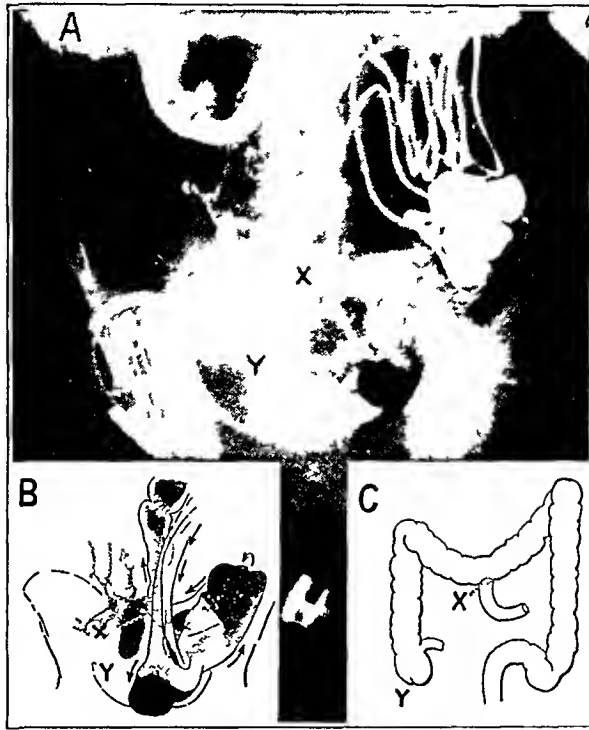


Fig 6—Partial obstruction for months due to recurrent regional ileitis (S B, aged 20). *A*, a roentgenogram taken after the injection of barium sulfate, showing filling of six fecal fistulas and the intestinal tube. *B*, a drawing reconstructing the intestinal relations as interpreted from the roentgenographic study. *C*, a drawing of the colon and ileum as they were left after the original ileocolostomy. The ileum entered the mid portion of the transverse colon by an end to side anastomosis, while the diseased stump of ileum remained in situ. In each figure *X* represents the ileocolostomy opening and *Y* the head of the cecum. It was apparent that the entire cecum, ascending colon and part of the transverse colon had contracted to form a chamber, between 10 and 15 cm in length, into which all the fistulas emptied. The obstruction was due to constriction of the ileum at the site of the ileocolostomy. By manipulation of the coils of intestine containing the tube it became evident that there was sufficient motility to bring sound ileum and colon together for a new ileocolostomy opening.

a situation calling for emergency measures into one in which the time of operation, if it is performed at all, becomes a matter of election. The great contraindication to intubation is the presence of gangrenous tissue. When that is absent, intubation temporarily controls the situation. One's success with the procedure, therefore, will be no better than one's clinical judgment. In cases of external hernia intubation is not necessary, likewise, in cases of low colonic obstruction, save in special instances. There remain occasional strangulated internal hernia, volvulus,

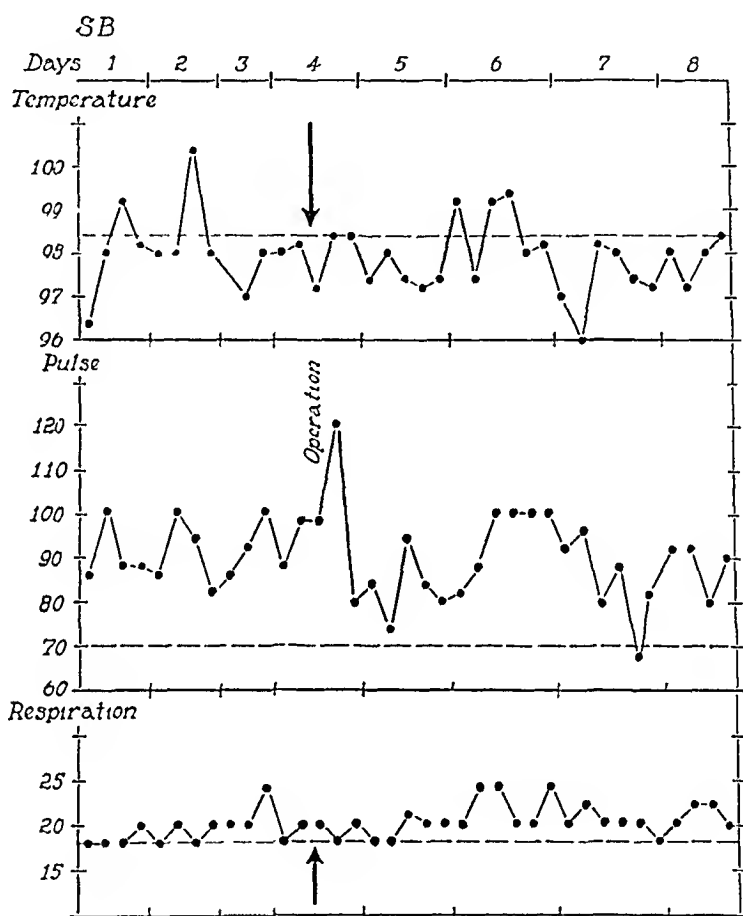


Fig 7—The clinical course recorded for S B (fig 6). The curves show the temperature, pulse rate and respiratory rate before and after the performance of ileocolostomy, with exclusion of the cecum. The intestinal tube was left in place so that constant suction could be maintained above the suture line. Since the intestine was thin at the point of anastomosis, the measure proved a real safeguard.

intussusception and mesenteric thrombosis as conditions productive of intestinal infarction. In all of them, however, the severity of the symptoms and the acute localized tenderness are likely to serve as a warning that a blood vessel has been occluded. Granted, however, that in such a case intubation is resorted to, there would be warning of danger by the failure of the symptoms to abate as decompression



TABLE 2—Summary of Data

Case and Initials	Age and Sex	Diagnosis	Duration of Obstruction	Degree of Obstruction	Character of Lesion	Number of Lesions	Duration of Intubation, Days	Operation After Intubation, Days	Period from Admission to Operation, Days	Outcome	Estimated Value of Intubation
Mechanical Obstruction											
1 H S	64 M	Pelvic abscess involving ileum, perforated recto sigmoid carcinoma	8 days	Complete	Inflammatory swelling of ileum	Single	9	0		Recovery	Cruel
2 J W	60 F	Rectosigmoid carcinoma	5 days	Complete	Annular carcinoma of sigmoid flexure	Single	6	Yes	6	Recovery	Rendered preliminary cecostomy unnecessary
3 J R	68 M	Carcinoma of sigmoid flexure	5± days	Partial	Annular carcinoma of sigmoid flexure	Single	3	Yes	12	Recovery	Very little, cecostomy required
4* D G	67 M	Prostatic carcinoma with uremia	2 days	Complete	Massive pelvic lesion	Single	1½	0		Death	Symptomatic relief only, death due to uremia
5 J W	44 M	Carcinoma of colon with peritoneal carcinomatosis	14 days	Partial	Wide metastases	Multiple	12	0		Partial recovery	Tided over acute episode
6 P B	50 F	Pelvic adhesions, pneumonia	4 days	Complete	Occlusion of ileum	Multiple	4	0		Recovery	Slight, balloon burst
7 S B	26 M	Recurrent ileitis with multiple abdominal fistulas	Weeks	Partial	Deformed colon and ileocolostomy	Multiple	4	Yes	Sever 1	Marked recovery	Very great
8 F D	36 M	Recurrent regional ileitis in terminal portion of ileum	{ 5 days 3 days	Partial Complete	Constricted terminal portion of ileum	Single	9	Yes	6	Recovery	Cruel
9 A H	63 M	Peritoneal adhesions	5 days	Complete	Bands of adhesions	Three	6	Yes	4	Recovery	Very great
10 V I	47 F	Pelvic adhesion	6 days	Almost complete	Dense perirectal adhesions	One	3	Yes	5	Recovery	Great
11 F B	60± F	Abdominal carcinomatosis	3 weeks	Partial	Diffuse serosal lesions	Multiple	3	0		Slow decline	Some symptomatic relief
12 F N	40 M	Abscess in abdominal wall	4 days	Partial	Adherence of ileum to abscessed wall	Single	3	Yes	3	Recovery	Great

		Omental adhesion	3 days	Complete	Intumescence by adhesion	Single	1	Yes	Recovery	Very great
11*	W S	17 M								
14	P I	23 I	1 d ys	Almost complete	Occlusion of ileum	Multiple	2	0	Some improvement	Tided over acute episode
15*	J K	73 M	1± days	Almost complete	Colonic obstruction	Single	1	Yes	Death	Deflated intestine and re-tored peristalsis
					Paralytic Obstruction					
16*	W S	47 M	5± days	Complete	Loeal peritonitis		7		Recovery	Critical
17*	I I	63 M	1 d ys	Complete	Postoperative ileus		5		Recovery	Very great
18	H X	35 J	6 days	Complete	General peritonitis		1½		Death	Restored intestinal function
19	O A	65 M	2 d ys	Complete	Peritoneal irritation		2		Death	Slight
20	J P	60 M	1 d ys	Complete	Postoperative ileus		11		Death	Restored intestinal function
21	S W	75 M	2 d ys	Complete	Postoperative ileus		4		Death	Partially restored intestinal function
					Failure to Pass the Tube Beyond the Duodenum					
22*	W B	70 M			Subphrenic abscess, fistulas to abdominal wall and to right bronchus, clatrictal stenosis of duodenum					
23*	I, D	72 J			Femoral hernia surgically corrected, intubation attempted at once with out success, no obstruction resulted					
24	M P	79 F			Megacolon with low obstruction, tension on gastrocolic omentum prevented intubation					
25	O R	63 M			Gastric carcinoma with peritoneal metastasis and multiple obstructions					
26	I S	40 M			Postoperative general peritonitis					
27	G H	52 M			Metastasis from colonic carcinoma, one mass involved the duodeno jejunal junction					

\* Cases previously reported

proceeded, and at any time the decision to operate could be made. On the other hand, when, after intubation in a case of obstruction, the pain and vomiting abate with the disappearance of distention, an enterostomy has been produced above the point of obstruction. True, the enterostomy tube leads through the nose rather than through the abdominal wall, but the advantages and dangers relative to the location, high or low, in the intestines are the same. With the fecal current diverted, a diet of strained soups, fruit juices, eggs, rare beef, farina, boiled or puffed rice, jelly and zwieback or crackers will go far to restore the calories, protein and electrolytes, while the nature of the lesion is being studied. The degree to which this has been possible is exemplified in table 2.

#### CONCLUSION

From these observations it may be concluded that intubation not only rarely adds to the hazards of acute intestinal obstruction but, on the contrary, frequently improves the clinical condition of the patient, increases his comfort, enables the physician to determine the characteristics of the obstructing lesion, simplifies its resection when that proves necessary, safeguards the convalescence and, above all, contributes to the safety of the patient by converting an emergency condition into a condition that is completely under the physician's control.

Tubing with a double lumen has been made for us by the U S Rubber Products Co., Passaic, N J, and the Lee Tire and Rubber Co., Conshohocken, Pa. A double-lumened tube, fully mounted for intubation of the small intestine, can be obtained through George P. Pilling & Son Co., Philadelphia. A  $\frac{1}{32}$  inch (1 mm) tube, suitable for inflating a balloon, is made by the Duval Rubber Co., Providence, R I.

# INFLUENCE OF EXERCISE ON CARDIAC OUTPUT IN CONGESTIVE HEART FAILURE

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AND

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CINCINNATI

It has been conclusively demonstrated that the cardiac output of a normal person is increased by exercise<sup>1</sup> Likewise, in persons with compensated heart disease the occurrence of an essentially normal increase in cardiac output after moderate exercise has been reported by several investigators<sup>2</sup> Hitherto no studies have been described concerning the influence of exercise on the cardiac output of patients with congestive heart failure The few studies relating to exercise and its influence on the cardiac output of patients with mild decompensation<sup>3</sup> (able to ride a bicycle or climb stairs) are of doubtful accuracy because of tech-

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1 (a) Grollman, A The Cardiac Output of Man in Health and Disease, Springfield, Ill, Charles C Thomas, Publisher, 1932, pp 129-137 (b) Bock, A V, Vancaulaert, C, Dill, D B, Folling, A, and Hurxthal, L M Dynamical Changes Occurring in Man at Work, *J Physiol* **66** 136, 1928 (c) Hochrein, M, Talbott, J H, Dill, D B, and Henderson, L J Die Bestimmung der Blutzirkulation im Ruhe und Arbeit, *Arch f exper Path u Pharmacol* **143** 147, 1929

2 Newburgh, L H, and Means, J H The Blood Flow in a Patient with Double Aortic and Double Mitral Disease, *J Pharmacol & Exper Therap* **7** 441, 1915 Alt, H L, Walker, G L, and Smith, W C Cardiac Output in Heart Disease The Effect of Exercise on the Circulation in Patients with Chronic Rheumatic Valvular Disease, Subacute Rheumatic Fever, and Complete Heart Block, *Arch Int Med* **45** 958 (June) 1930 Meakins, J, Dautrebande, L, and Fetter, W J The Blood Gases and Circulation Rate in Cases of Mitral Stenosis, *Heart* **10** 153, 1923 Liljestrand, G, and Zander, E Studies of the Work of the Heart During Rest and Muscular Activity in a Case of Uncomplicated Total Heart Block, *Acta med Scandinav* **66**.501, 1927

3 Bansi, H W, and Groscurth, G Kreislauffunktionsprüfung bei Herzkranken, *Deutsche med Wchnschr* **57** 1276, 1931 Nielsen, H E Clinical Investigations into the Cardiac Output of Patients with Compensated Heart Disease During Rest and During Muscular Work, *Acta med Scandinav* **91** 223, 1937

nical difficulties inherent in the older methods for determination of the cardiac output in the presence of pulmonary congestion <sup>4</sup>

Since the inability of a patient with organic heart disease to increase adequately the cardiac output with effort may be an important factor in the pathogenesis of congestive heart failure, we have compared the cardiac output after moderate, measured exercise of (1) patients with congestive heart failure, (2) patients with well compensated heart disease and (3) control subjects

#### METHOD

The three sample acetylene method of Grollman as modified by Grollman, Friedman, Clark and Harrison <sup>5</sup> for measurement of cardiac output in cases of congestive heart failure was employed for the determination of the basal cardiac output and the cardiac output following work

The determinations of cardiac output for the majority of the patients with cardiac decompensation were carried out on the second or the third day after their admission to the hospital, when diminution of dyspnea made cooperation possible. All the patients with congestive heart failure were receiving digitalis. As digitalis has been reported to increase the output of the dilated heart <sup>6</sup> or to have no constant influence on it,<sup>7</sup> the low values for cardiac output obtained for patients suffering from decompensation were probably not related to administration of digitalis

The patients with compensated heart disease had all suffered from one or more previous episodes of congestive heart failure. The control subjects were of various ages and in varying stages of physical fitness. The patients with cardiac decompensation had entered the hospital because of symptoms of congestive heart failure. Data concerning the patients in the three groups are summarized in the accompanying table

Each patient was studied under basal conditions. The oxygen consumption was determined with the Benedict-Roth metabolism apparatus while the patient was sitting upright in bed. Relaxation and comfortable position were provided by placing several pillows behind the head and back. After measurement of the basal oxygen consumption, determination of the cardiac output with the patient

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4 Grollman,<sup>1a</sup> pp 48-51

5 Grollman, A, Friedman, B, Clark, G, and Harrison, T R. Studies in Congestive Heart Failure. XXIII. A Critical Study of Methods for Determining the Cardiac Output in Patients with Cardiac Disease, *J Clin Investigation* **12** 751, 1933

6 Stewart, H J, and Cohn, A E. Studies on the Effect of the Action of Digitalis on the Output of Blood from the Heart. III. The Effect on the Output in Normal Human Hearts. The Effect on the Output of Hearts in Heart Failure with Congestion in Human Beings, *J Clin Investigation* **11** 917, 1932. Starr, I, Gamble, C J, Margolies, A, Donal, J S, Joseph, N, and Eagle, E. A Clinical Study of the Action of Ten Commonly Used Drugs on Cardiac Output, Work and Size, on Respiration, on Metabolic Rate and on the Electrocardiogram, *ibid* **16** 799, 1937

7 Harrison, T R. Failure of the Circulation, Baltimore, Williams & Wilkins Company, 1936

# *Influence of Exercise on the Cardiac Output*

Patient	Sex	Condition	At Rest						After Exercise											
			Arterial Blood Pressure, Mm Hg	Pulse Rate	Circulation Time, Sec	Vital Capacity, Per centage of Normal	Oxygen Consumption per Minute, Cc	Basal Metabolic Rate, Percentage	Arteriovenous Oxygen Difference per Liter, Cc	Cardiac Output per Minute, Liters	Stroke Volume, Cc	Work Done, Kilogram meters per Minute	Arterial Blood Pressure, Mm Hg	Pulse Rate	Oxygen Consumption per Minute, Cc	Arteriovenous Oxygen Difference per Liter, Cc	Cardiac Output per Minute, Liters	Stroke Volume, Cc	Increase in Cardiac Output per Minute, Liters	
			Normal																	
K I	♂	Peripheral neuritis with foot drop	170/110	84	20	90	236	-3	36.0	4.22	70	22.2	165/110	65	319	27.5	9.6	71	2.11	
A N	♂	Convalescent from hernia	110/80	78	26	85	204	-10	67.2	3.04	6	18.5	125/90	81	268	17.5	18.1	57	1.77	
I Q	♂	Normal	98/78	72		96	225	-12	62.3	3.61	50	19.8	110/80	96	342	60.3	3.17	54	1.56	
G S	♀	Neurocirculatory asthenia	110/70	84		73	185	-1	72.5	3.73	42	19.8		90	304	12.3	5.75	61	2.22	
I D	♂	Normal	100/70	69	20	113	231	-1	66.0	3.51	51	19.8	100/70	72	285	47.7	3.61	58	2.46	
With Compensated Heart Disease																				
W I	♂	Arteriosclerotic heart disease with hypertrophy	176/120	72	29	77	288	+24	88.2	3.27	45	19.8	180/130	78	110	74.0	5.10	65	1.43	
W T	♂	Hypertrophic heart disease	200/88	72	17	60	371	+45	75.0	4.95	69	20.1	200/100	66	510	95.0	5.93	90	1.00	
H M	♂	Rheumatic heart disease mitral stenosis, aortic insufficiency	110/60	96	25	56	234	+25	80.5	2.90	30	20.0	150/64	90	304	68.0	4.20	47	1.40	
I O	♂	Aortic stenosis and insufficiency, mitral stenosis and insufficiency	130/60	90	34	310	438	+38	80.0	3.52	39	19.8	180/0	111	361	9.5	4.22	5	0.70	
With Decompensation																				
E B	♂	Syphilitic aortitis, aortic insufficiency	140/56	96	34	70	250	+12	91.0	2.79	29	22.2	140/48	108	335	9.6	4.10	1	0.61	
A P	♂	Arteriosclerotic and hypertrophic heart disease	160/130	112	72	367	231	+30*	120.3	2.11	21	19.8	180/110	120	345	113.0	3.15	26	0.81	
H D	♂	Coronary heart disease	120/100	78	33	53	196	-15	107.0	1.81	23	19.8	138/100	110	294	105.0	2.52	21	0.71	
M T	♀	Aortic insufficiency, syphilitic aortitis	126/80	126	28	37	186	+2	78.5	2.34	18	20.0	126/70	126	257	79.2	3.16	25	0.82	
M B	♀	Syphilitic and hypertrophic heart disease, general vascular sclerosis	190/96	90		31*	273	-5*	80.5	2.53	26	18.9	180/86	102	328	83.5	3.19	31	0.83	
									102.0							113.0				

\* See note of peripheral edema; the determination of body surface in square meters was approximated  
 + Oxygen consumption was measured during, not after, exercise

at rest was carried out. The subject then remained at complete rest for one-half hour or longer, and a second determination of the oxygen consumption for a three minute period was made.

Both normal control subjects and patients were then required to perform a similar exercise for two minutes. Measurement of oxygen consumption was continued throughout the exercise period. This consisted of lifting in each hand a dumbbell weighing  $1\frac{1}{2}$  pounds (0.7 Kg) to a measured height (97 to 100 cm) fourteen to eighteen times per minute. The work ranged from 185 to 222 kilogrammeters per minute. The variable length and weight of the arms were disregarded in calculation of the work performed. This exercise was selected because it was sufficiently mild for patients with congestive heart failure. Moderate dyspnea occurred in each case, but only a slight effect was observed on the frequency and depth of the respirations of the normal subjects.

At the end of the two minute period of work the subject was connected with the portable acetylene apparatus, and the cardiac output was determined. Not more than twenty seconds elapsed in any case between the discontinuation of the work and the beginning of the test. Rapid circulation in the normal group and slow circulation in the group with cardiac disease necessitated collection of the samples at differing times during the experimental procedure. For the patients with cardiac disease our guide for the proper time for collection of samples was the basal circulation time as determined by the sodium cyanide method.

From the normal subjects samples 1, 2 and 3 were collected on the fourth, sixth and eighth expirations, respectively, and the last sample on the fifteenth second of rebreathing. From the patients with compensated heart disease samples 1, 2 and 3 were collected on the fourth, sixth and eighth expirations, respectively, in some cases and on the fifth, seventh and ninth expirations in others, the last sample being obtained between the thirteenth and the nineteenth second of rebreathing. From the patients with decompensation samples 1, 2 and 3 were collected on the seventh, ninth and eleventh expirations in some and on the sixth, eighth and tenth expirations in others and the last sample between the nineteenth and the twenty-third second of rebreathing.

When the arteriovenous oxygen differences between samples 1 and 2 and samples 2 and 3 were within 10 per cent, we assumed that adequate mixing had occurred and that recirculation had not occurred. Occasionally the third sample was collected too late, recirculation having occurred. This became evident if the arteriovenous oxygen difference between samples 2 and 3 was considerably greater than that between samples 1 and 2, and when this occurred the determination was disregarded.

## RESULTS

The effects of exercise on cardiac output, stroke volume, oxygen consumption and arteriovenous oxygen difference of the normal subjects, the patients with compensated cardiac disease and the patients with decompensation are summarized in the table. The changes in cardiac output are indicated in charts 1 and 2.

For the controls the average increase in cardiac output following exercise was 2.07 liters per minute, for the patients with compensated heart disease, 1.21 liters per minute, and for patients with decompensation, 0.75 liter per minute. The work performed, as measured in kilogrammeters per minute, was essentially the same for each group.

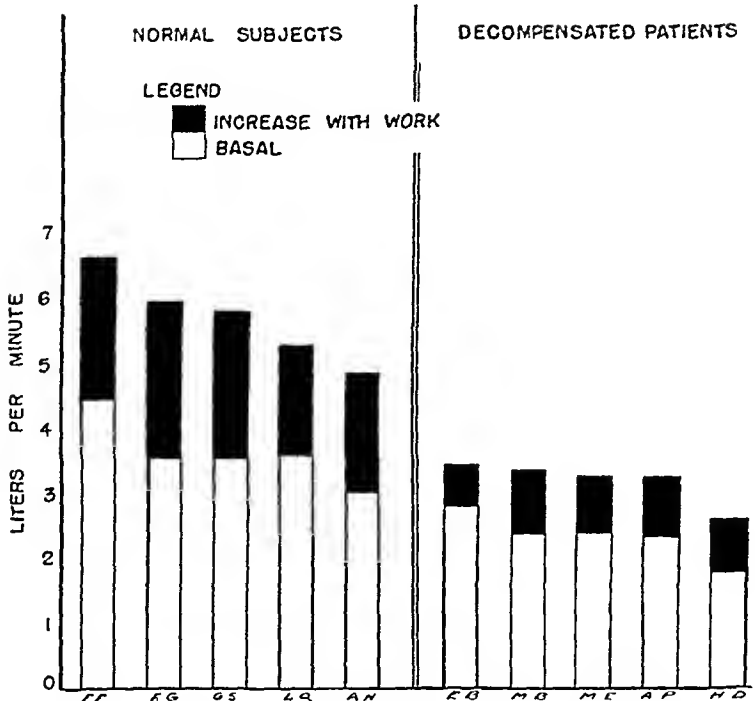


Chart 1—Cardiac output at rest and after exercise

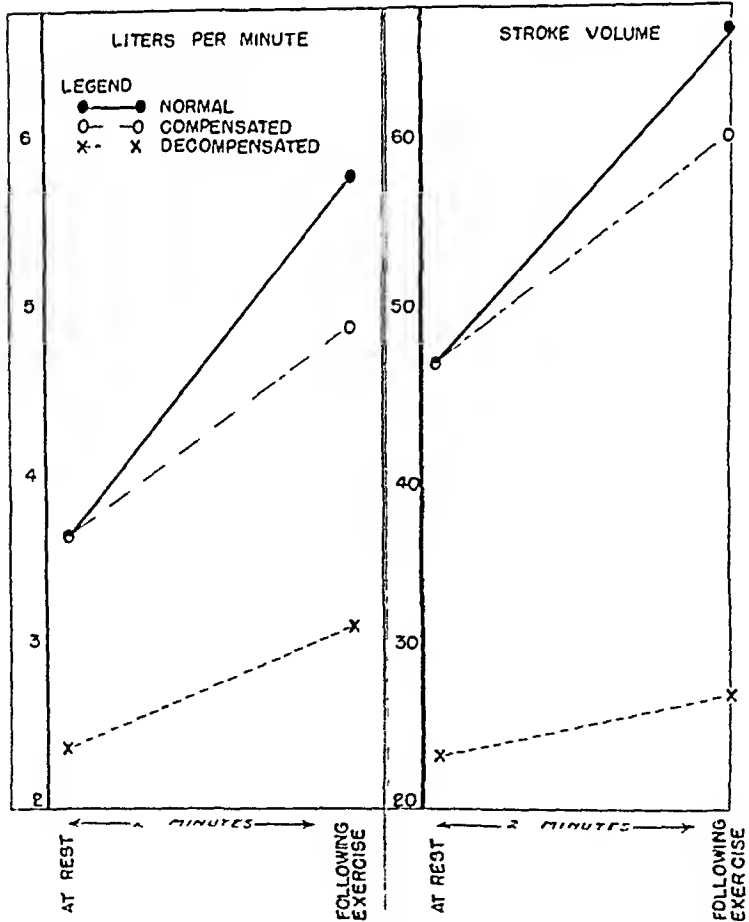


Chart 2—Average cardiac output at rest and after exercise



The average stroke volume of the normal subjects increased 19 cc per beat after work, for the patients with compensated cardiac disease there was an average increase of 14 cc per beat, for the patients with cardiac decompensation there was an average increase of only 4 cc per beat

No constant change in the arteriovenous oxygen difference following exercise occurred in any of the groups

For the normal subjects the average increase in oxygen consumption with work was 148 cc per minute, for the patients with compensated cardiac disease it was 111 cc per minute, and for the patients with cardiac decompensation only 92 cc per minute

The pulse rate was accelerated moderately after exercise in the normal subjects and in the patients with decompensation

However, we were surprised to find no acceleration of the pulse rate after exercise in 2 of the patients with compensated cardiac disease. Perhaps inadequate coronary blood flow may have been responsible. Failure of acceleration of the rate of the heart after exercise in patients with disease of the coronary arteries has been reported by Biering, Laisen and Nielsen.<sup>8</sup>

We have made no extensive study of the influence of strenuous exercise on cardiac output. However, in 1 patient with congestive heart failure who was asked to exercise by lifting the dumb-bells until dyspnea forced him to discontinue the procedure, the cardiac output increased only 1.05 liters per minute. With similar exercise of three minutes' duration 1 of the normal subjects increased his cardiac output by 3.51 liters per minute—a difference of 250 per cent, indicating that strenuous exercise of this character did not cause the cardiac output of the patient with decompensation to increase in a normal manner.

#### COMMENT

Experimental evidence for the validity of the acetylene method of measuring the cardiac output after exercise in normal persons has been reported by Bansi and Groscurth.<sup>9</sup> Grollman likewise concluded that the method is accurate during exercise if the cardiac output is not increased to more than 10 liters per minute.<sup>10</sup> Comparative studies with the acetylene and the direct Fick method have shown close parallelism of results for patients with cardiac decompensation under

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8 Biering, E., Larsen, K., and Nielsen, E. Some Cases of Slow Pulse Associated with Electrocardiographic Changes in Cardiac Patients After Maximal Work on Krogh Ergometer, *Am Heart J* **11** 416, 1936

9 Bansi, H. W., and Groscurth, G. Die Bestimmung des zirkulatorischen Minutenvolumens mittels Acetylen nach Grollman in der Ruhe und bei Arbeitsversuchen, *Ztschr f d ges exper Med* **77** 631, 1931

10 Grollman, A. Personal communication to the authors

basal conditions, although the absolute values tended to be lower when the acetylene method was used<sup>11</sup> As the mild exercise employed in this study caused no marked increase in cardiac output (less than 10 liters) and because of the safeguards of the three sample acetylene method in detecting recirculation, we believe that the measurements of blood flow after exercise have yielded significant values, though we fully realize that the method used, like all indirect methods, is not accurate to the cubic centimeter

#### SUMMARY

The influence of similar measured exercise on the cardiac output of 5 normal subjects, 4 patients with compensated cardiac disease and 5 patients with cardiac decompensation has been determined

In the normal subjects a considerable increase in cardiac output with exercise occurred, the average increase being 2.07 liters per minute

In the patients with compensated cardiac disease the increase in cardiac output was moderate, the average increase being 1.21 liters per minute

In the patients with congestive heart failure the increase in cardiac output with exercise was small, the average increase being 0.75 liter per minute

These data suggest that in patients with severe cardiac decompensation under the conditions of these experiments the cardiac output is not increased with effort to the same degree as it is in normal persons and that relative inability to increase the cardiac output may have an important bearing on the pathogenesis of congestive heart failure

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11 McGuire, J, Shore, R, Hauenstein, V, and Goldman, F Relation of Cardiac Output to Congestive Heart Failure, *Arch Int Med* **63** 290 (Feb) 1939

# DERMATOMYOSITIS WITH SCLERODERMA, CALCINOSIS AND RENAL ENDARTFRITIS ASSOCIATED WITH FOCAL CORTICAL NECROSIS

REPORT OF A CASE IN WHICH THE CONDITION SIMULATED  
ADDISON'S DISEASE, WITH COMMENT ON METABOLIC  
AND PATHOLOGIC STUDIES

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The clinical similarity between Addison's disease and the syndrome recognized as dermatomyositis with scleroderma may be marked. Confusion regarding the differential diagnosis is likely and has been discussed by Osler,<sup>1</sup> Winfield,<sup>2</sup> Boardman,<sup>3</sup> Longcope,<sup>4</sup> Rowntree and Snell,<sup>5</sup> Brown and his associates,<sup>6</sup> Howard,<sup>7</sup> and others. The coexistence of these two diseases must be extremely uncommon, and the contemporary

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From the Medical Clinic, the Laboratory of Pathology and the Laboratory of Bacteriology of the Massachusetts General Hospital, and from the Fatigue Laboratory, Harvard University

1 Osler, W. On Diffuse Scleroderma, with Special Reference to Diagnosis, and to the Use of the Thyroid-Gland Extract, *J Cutan & Genito-Urin Dis* **16** 127, 1898

2 Winfield, J M. A Case of Scleroderma, *J Cutan & Genito-Urin Dis* **22** 586, 1904

3 Boardman, W P. Scleroderma, with Special Reference to Its Etiology and Treatment, *Arch Dermat & Syph* **19** 901 (June) 1929

4 Longcope, W T. Hypoglycemia in Scleroderma. The Metabolism in Eight Cases with Reference to the Function of the Glands of Internal Secretion, *J A M A* **90** 1 (Jan 7) 1928

5 Rowntree, L G, and Snell, A M. A Clinical Study of Addison's Disease, Philadelphia, W B Saunders Company, 1931

6 Brown, G E, O'Leary, P A, and Adson, A W. Diagnostic and Physiologic Studies in Certain Forms of Scleroderma, *Ann Int Med* **4** 531, 1930

7 Howard, C P. Scleroderma with Calcinosis, *Canad M A J* **37** 124, 1937

literature contains few reliable reports. Lewin and Heller<sup>8</sup> in a review of 508 cases of scleroderma reported before 1895 noted that the dual diagnosis had been made in only 4. Osler<sup>1</sup> reviewed these cases and did not consider that any of the patients had Addison's disease. In 1908 Lichtwitz<sup>9</sup> reported a single case in which the two diseases coexisted clinically, the observation was confirmed at autopsy. Recently Leriche, Jung and De Bakey<sup>10</sup> reported the occurrence of Addison's disease in a patient under treatment for scleroderma. Autopsy was not performed, however, and the diagnosis can be accepted only with reservation.

In this communication we shall report clinical, metabolic and pathologic observations on a woman who was admitted to the hospital with a presumptive diagnosis of Addison's disease. Suspicion of adrenal insufficiency was based on a history of profound weakness and malaise, gastrointestinal disturbances, loss of weight and pigmentation of the skin. On physical examination there was postural hypotension. Laboratory studies showed a diminished concentration of total base and of sodium in the serum and an increased concentration of nonprotein nitrogen. A negative chloride balance and a positive potassium balance were observed while the patient was under a metabolic regimen. The patient improved in a satisfactory manner with a high salt intake and rest in bed. During this treatment, however, the skin became shiny, taut and atrophic, and the presence of dermatomyositis with scleroderma became apparent. Eleven months after the onset of symptoms and three months before death subcutaneous nodules were palpable, and roentgen examination revealed calcinosis. At postmortem examination the adrenal glands were normal in size and appearance. The significant anatomic diagnoses were chronic nonsuppurative dermatomyositis, scleroderma, calcinosis and obliterative endarteritis of the kidneys.

During the first period of hospitalization, while the patient was under observation in the metabolic ward, studies of the electrolyte balance were completed. One year later, a month before death, she was observed a second time in the same ward, and the studies were repeated. Observations of the acid-base balance of the blood were made at frequent intervals during the illness and on the day of death.

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8 Lewin, G., and Heller, J. *Die Sclerodermie. Eine monographische Studie*, Berlin, A. Hirschwald, 1895.

9 Lichtwitz, L. Ueber einem Fall von Sklerodermie und Morbus addisonii nebst Bemerkungen über die Physiologie und Pathologie des Sympathicus und der Nebennieren, *Deutsches Arch. f. klin. Med.* **94** 567, 1908.

10 Leriche, R., Jung, A., and De Bakey, M. *The Surgical Treatment of Scleroderma*, Surgery **1** 6, 1937.

## REPORT OF CASE

H T W, a Canadian-born woman aged 26, a housewife, was admitted to a ward in the Massachusetts General Hospital on Dec 7, 1935, with a tentative diagnosis of Addison's disease

The family history revealed that the mother had died of tuberculous meningitis at the age of 46, eight years after she had been treated in a sanatorium for pulmonary tuberculosis. The patient had lived at home with her mother during this time

The past history contained nothing of significance before the onset of the present illness. The patient had considered herself a strong, healthy girl and had been unusually free from minor illnesses. Before marriage she had worked in a box factory. No unusual occupational hazard was recognized during this employment

The patient had been married for eighteen months. Four months prior to her admission to the hospital, after an uneventful pregnancy, she had given birth at full term to a normal child. During the antepartum period she had visited her family physician twice a month. At each visit the blood pressure was within the normal range. A trace of albumin was found in the urine on more than one examination. Because of this finding she was advised to restrict her salt intake during the last three months of pregnancy

The present illness began about six weeks after delivery. She noted that her legs were weak and tired when she walked outdoors, although her strength seemed good while she was engaged in similar activity in the house. The weakness in the legs progressed, however, and she began to conserve her energy indoors as well. In climbing a flight of stairs she would often rest once or twice before she reached the top. Shortly after this she noticed some difficulty in extending her arms, and weakness, which had been confined to the legs, appeared in the upper extremities. There were no symptoms suggesting sensory or motor disturbance, and no fibrillary twitching of the muscles was noted

One month before her admission to the hospital her friends observed a deep suntan-like pigmentation of the skin, although she had had no prolonged exposure to the sun for several months. Shortly after this, because of extreme weakness she was forced to give up all her household duties and would lie down or sit most of each day. Her appetite was good except on certain days, when she vomited recently ingested food. After her pregnancy she had menstruated normally three times. She had skipped one period immediately preceding entry. She had lost about 20 pounds (9.1 Kg) in weight. Her family physician made a tentative diagnosis of pellagra because of the pigmentation. Dr Albert H Covner, of Lynn, Mass, was consulted and made a presumptive diagnosis of Addison's disease. He referred her to the Massachusetts General Hospital

Physical examination showed a poorly nourished woman of slender stature. Patchy areas of pigmentation were superimposed on a skin, which seemed darker than usual for a blond. The deeply pigmented areas were principally around the breasts, in the axillary folds and on the abdomen and the buttocks. There was no increased pigmentation of the mucous membrane of the mouth. The elbows could be extended through an arc of only about 110 degrees and the knees through an arc of about 90 degrees. The skin about these joints was slightly taut. No other pathologic changes in or about the joints were noted. The blood pressure with the patient lying down was 120 systolic and 80 diastolic, and with the patient standing, 86 systolic and 70 diastolic

*Clinical Laboratory Data*—The specific gravity of the urine was 1.024. No sugar, albumin or blood cells were noted at either of two examinations. The red blood cell count was 4,870,000, the leukocyte count, 10,200. The differential count showed 63 per cent polymorphonuclears, 32 per cent lymphocytes, 4 per cent eosinophils and 1 per cent basophils. The Hinton reaction of the blood was negative. The basal metabolic rate at two determinations was +18 and +5 per cent, respectively. There was no free hydrochloric acid in the gastric contents one hour after injection of 0.5 mg of histamine phosphate U. S. P. and ingestion of 50 cc of 7 per cent alcohol.

The concentration of sodium in the serum was 127.3 milliequivalents per liter, the concentration of protein was 7.9 Gm per hundred cubic centimeters and the concentration of nonprotein nitrogen was 52 mg per hundred cubic centimeters.

*Röntgen Examination*—The following interpretations were reported by Dr. J. R. Lingley: "Examination of the chest shows no evidence of disease. A flat plate of the abdomen and films of the renal region show no significant changes from the normal."

*Course During First Period of Hospitalization*—A tentative diagnosis of Addison's disease and scleroderma was made, and the patient was transferred to the metabolic ward for further study. The electrolyte exchange with a metabolic regimen showed a negative chloride balance and retention of potassium. These observations appeared to confirm the diagnosis of adrenal insufficiency. The patient improved with a high intake of sodium chloride, and the concentration of sodium in the serum returned to normal.

Approximately one month later cutaneous atrophy in an early stage was noted, and the limitation of articular motion increased. At this time lumbar puncture was done, and because of unexpected findings this was repeated on three occasions. The initial pressure varied between 80 and 150 mm of water. The fluid was always clear, and no clot was demonstrated. There were never more than 3 white blood cells per cubic millimeter. The concentration of total protein varied between 67 and 105 mg per hundred cubic centimeters. The concentration of sugar varied between 63 and 67 mg. The colloidal gold curve at each determination was approximately 5555433210. The Wassermann reaction of the spinal fluid was negative.

A neurologic consultant made the following observations: "There is generalized muscular weakness of the voluntary muscles but no evidence of muscular atrophy, spasticity or flaccidity. There are no involuntary movements. All reflexes except the abdominal reflexes are present and normal."

A biopsy of the skin was reported by Dr. Charles S. Kubik as follows: "There are well marked degeneration and fibrosis of the corium, with extensive infiltration by lymphocytes, plasma cells and a small number of monocytes. The findings are similar to those observed in some cases of muscular weakness associated with arthritis and scleroderma."

The patient remained in the hospital more than three months. The rectal temperature fluctuated between 99 and 101 F. The daily fluctuations were intermittent at times and during two periods suggested a Pel-Ebstein type of fever. The pulse rate varied between 90 and 100 and the respiratory rate between 20 and 24. The postural hypotension persisted. The average blood pressure with the patient lying down was about 100 systolic and 70 diastolic and with the patient standing was about 90 systolic and 70 diastolic. During hospitalization she had remissions and relapses, but it was believed that the disease was becoming progressively worse when she was discharged, on March 7, 1936.

*Interval History*—During the succeeding five months the patient became weaker and spent more and more time in bed. The limitation of motion of the elbows and knees increased, presently involving the lumbar and the dorsal portion of the spine. She was advised to continue to take 10 Gm of sodium chloride in capsules each day but soon became discouraged and did this irregularly. In June 1936 she noted soreness of the mouth and tongue, associated with a failing appetite. Early in August she became so weak that she remained in bed continually. On advice she entered the hospital for further study on August 21.

*Second Admission*—Physical examination showed the following changes which had developed since her discharge from the hospital. The skin was atrophic and shiny over most of the body. It was dry and scaly. The face was pinched, drawn and pale. There was limitation of motion in the joints of all extremities and of the lumbar and the dorsal portion of the spine. A few hard subcutaneous nodules were present in the right axillary fold. Elsewhere subcutaneous nodules were not felt, because of the tenseness of the skin. There appeared to be generalized atrophy of the facial, truncal and skeletal muscles. The temperature, the pulse rate and the respiratory rate were similar to those observed during the first period of hospitalization.

*Laboratory Data*—The specific gravity of the urine was 1.029. No abnormal constituents were noted. The red blood cell count was 4,280,000, the leukocyte count, 9,000. The blood smear was normal. The basal metabolic rate at two examinations was +3 and +1 per cent, respectively. The colloidal gold curve was unchanged.

*Roentgen Examination*—The following report was made: "There has been no change in the appearance of the chest since the previous examination. Roentgenograms of the shoulder show calcification in the soft tissues of the axillary folds. Examination of the elbows shows extensive linear calcification in the soft tissues on their medial aspects. The right hand shows an area of calcification between the thumb and the index finger. Both legs show calcification in the soft tissues on the lateral aspects of the fibula, and both feet show calcification between the first and the second metatarsal bone. There is no evidence of sclerodactylia."

*Course During Second Period of Hospitalization*—The patient was transferred to the metabolic ward on October 29 and was observed for three five-day periods during which she was given a diet low in calcium, with 10 Gm of sodium chloride added. One week before death the specific gravity of the urine failed to exceed 1.010, and the excretion of 0.6 mg of phenolsulfonphthalein injected intramuscularly was 7 per cent in the first twenty-five minutes and 39 per cent after two hours and ten minutes. The patient continued to grow weaker, and she died on November 30.

*Gross Postmortem Examination*—The skin of the entire body was thickened, taut and glossy. There was brown pigmentation, more pronounced in the natural folds of the skin. The interosseous muscles were atrophied, and the hands showed ape-like configuration.

The subcutaneous fat was scanty and indurated. Within the panniculus and the connective tissue planes throughout the body there were numerous opaque, white, granular, calcium-like deposits, the largest of which were 2 cm in diameter. The skeletal muscular tissue was universally thinned and atrophic and because of its pallor had the appearance of uncooked breast of chicken.

The serous coats exhibited normal color and unimpaired sheen. The peritoneal cavity contained 2,000 cc, each pleural cavity 250 cc and the pericardium 340 cc of relatively clear yellowish fluid.

The upper lobe of the left lung contained a few peripherally situated, partially circumscribed fibrosed nodules measuring up to 0.5 cm in diameter. Except for moderate congestion and focal atelectasis the remainder of the pulmonary substance was normal.

No evidence of residual thymic tissue was observed within the mediastinum.

The heart weighed 240 Gm. The myocardium was pale but normal in consistency. The wall of the right ventricle measured 0.2 cm in thickness, and the left, 1.2 cm.

The aorta and the large arteries contained a few scattered noncalcified, atheromatous plaques measuring up to 0.5 cm. The vascular walls were thin, but the elasticity was unimpaired.

The liver weighed 1,680 Gm. Its surface was pale reddish brown, it was smooth and its substance was firm but moderately friable. The lobules were pale, and the central veins were prominent and engorged.

The spleen weighed 150 Gm. The cut surface was firm and the removable pulp diminished. The follicles were unusually prominent.

The adrenal glands weighed together 20 Gm. They were of normal appearance.

The kidneys weighed together 200 Gm. The capsules stripped without difficulty and revealed yellowish red mottled surfaces. The surfaces were irregularly ridged and furrowed. The furrows measured less than 1 mm in breadth, and the ridges, the surfaces of which were smooth, measured up to 5 mm. On section the cortex measured 4 to 6 mm. The areas subjacent to the surface depressions were paler than the remainder of the parenchyma. Although circumscribed, these pallid foci were not sharply demarcated and revealed no regular configuration. They did not extend throughout the entire depth of the cortex, and corticomedullary demarcation was normal.

All other organs, including the central nervous system, were examined and observed to be grossly normal.

Culture of blood from the heart at necropsy was sterile.

*Microscopic Postmortem Examination*—Adrenals. Multiple sections showed no pathologic changes.

*Skin*. The epidermis was thinned, the rete pegs were flattened and broadened, and the basal layer contained an increased amount of brown granular pigment. The corium contained a few pigment-bearing phagocytes but no significant inflammatory exudate. Superficially the dermis manifested a thin layer with a fibrillar edematous appearance. In the deeper layers (fig 1) the collagen was thickened and increased in amount, with diminution in the number of blood vessels and coil glands. Within the subcutaneous fat there were increased numbers of interlacing strands of fibrous tissue. Constituent collagen was focally swollen and poorly stained and exhibited granular fragmentation, with infiltration by hemosiderin-laden macrophages and abundant foam cells. Many foci of foam cells were present in otherwise unchanged fat, and there were also varying amounts of amorphous and granular eosinophilic substance as well as deeply basophilic spicules and blocks of calcified material. Calcification was accompanied by the presence of numerous monocytes and multinucleated foreign body giant cells and was most pronounced in the deeper portions of the panniculus overlying the diseased muscles.

*Skeletal Muscle*. The sections included pharyngeal, esophageal and diaphragmatic muscle as well as specimens from muscles of the extremities. The changes were spotty but widespread, and the lesions were variable. All areas manifested different phases, and some areas, all stages of severe myositis. There



was profound variability in the caliber of the muscular fasciculi, and many showed shrinkage, with wide separation from the perimysium. Occasionally the bundles were eosinophilic, swollen and lacking in striation. The majority, however, were frayed, and there was separation of the myofibrillae. Isolated muscular strands displayed marked nuclear proliferation, others were totally replaced by fibrous scar. There were scattered foci of lymphocytic infiltration (fig 2) distributed perivascularly and also within the interstitial tissue. In some regions the lymphoid exudate actually replaced disintegrating muscle substance, and pseudofollicle forma-

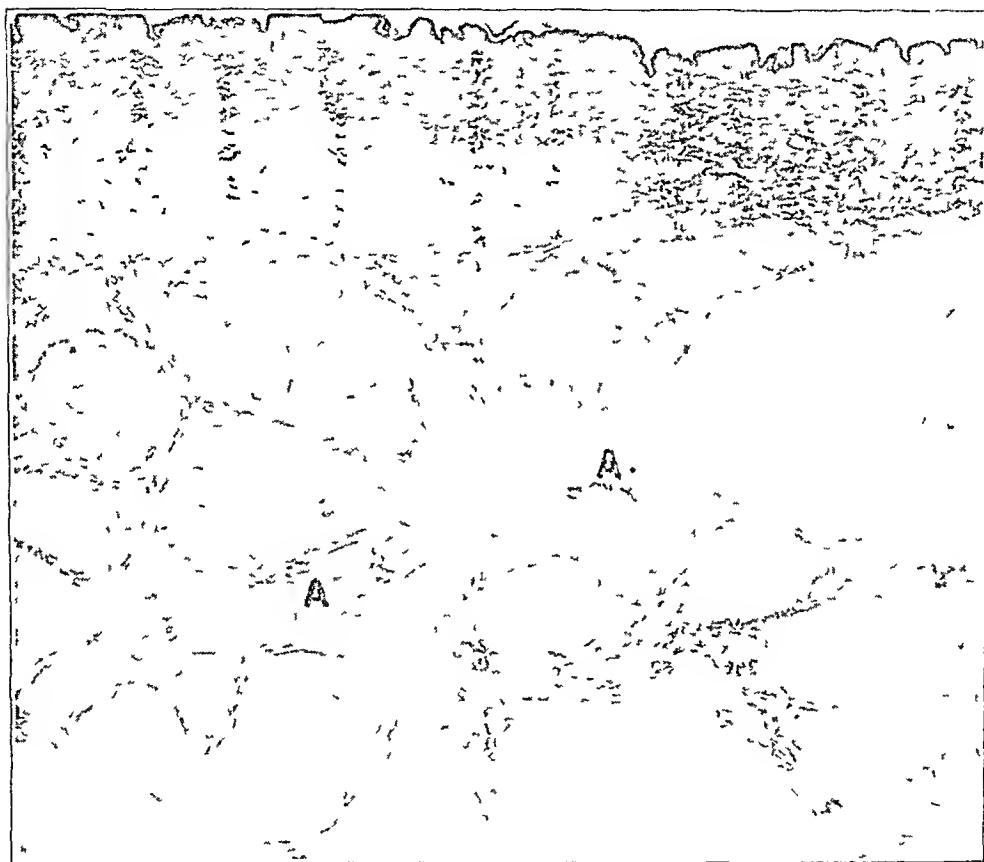


Fig 1—Skin, showing the narrow epidermis and dense, compact, relatively avascular dermis. The subcutaneous tissue exhibits interlacing fibrous strands and foci of calcification (A).

tion was observed. The noteworthy feature of the muscular changes was the extent as well as the degree of the involvement.

**Peripheral Nerve** The sections examined showed no significant changes within the fibrillae. Irregularly distributed, however, in the perineural sheath were small aggregations of lymphocytes and plasma cells.

**Kidney** The histologic appearance was, in our experience, unique. Examination of the cortex by means of low power magnification revealed an alteration of foci of relatively normal architecture, with narrow bands of atrophic tissue corresponding to the depressions noted in the gross examination. Glomeruli appeared to be evenly distributed through both the normal and the atrophic areas.

(fig 3), but in the latter the tubules were entirely different. Instead of the usual large, conspicuous convoluted tubules with narrow lumens clustered about the glomeruli, there were only small tubules lined with low cuboidal cells which stained intensely with dye for basophilic material. The appearance simulated that of malfunctioning fetal tubules, a phenomenon of regeneration previously noted by Kaufmann,<sup>11</sup> Maatz<sup>12</sup> and Mallory.<sup>13</sup> All evidence of brush border was lacking. The normal convoluted tubules were separated from each other by a rich capillary network and only a delicate reticulum. The abnormal tubules were embedded in abundant, fairly dense and relatively avascular fibrous stroma

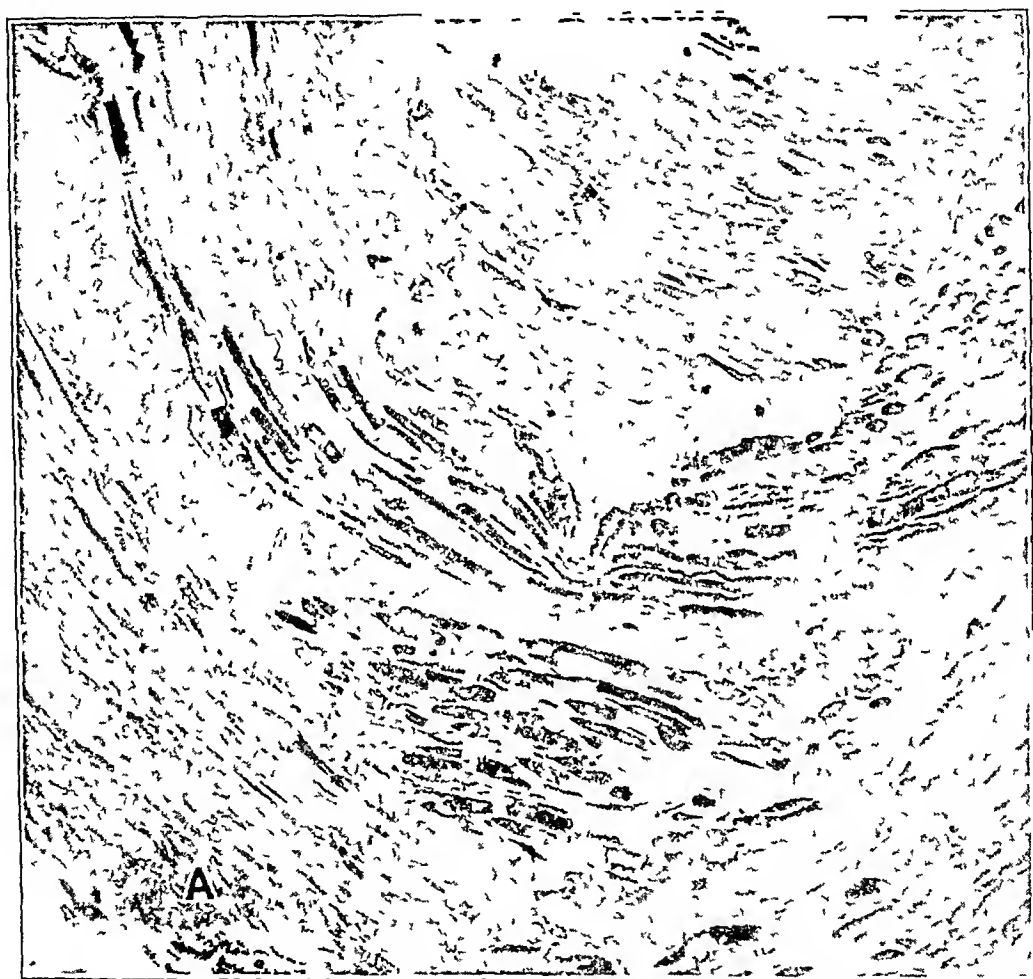


Fig 2—Skeletal muscle, showing variability of staining power, irregular replacement by fibrous tissue and focal aggregation of lymphocytes (A)

Careful inspection of the apparently normal areas showed that in them also there were focal areas of degeneration. Groups of convoluted tubules showed coagulation necrosis of the epithelium, loss of staining power of the nuclei and

11 Kaufmann, E. *Lehrbuch der speziellen pathologischen Anatomie für Studierende und Aerzte*, Berlin, E. de Gruyter & Co., 1922, vol 2, p 109

12 Maatz, R. Experimentelle tubuläre Schrumpfnieren durch vorübergehende Gefäßabklemmung, *Frankfurt Ztschr f Path* **46** 438, 1934

13 Arteriosclerosis, Generalized, Marked Aortic, Coronary and Renal. Cabot Case 23041, *New England J Med* **216** 170 1937

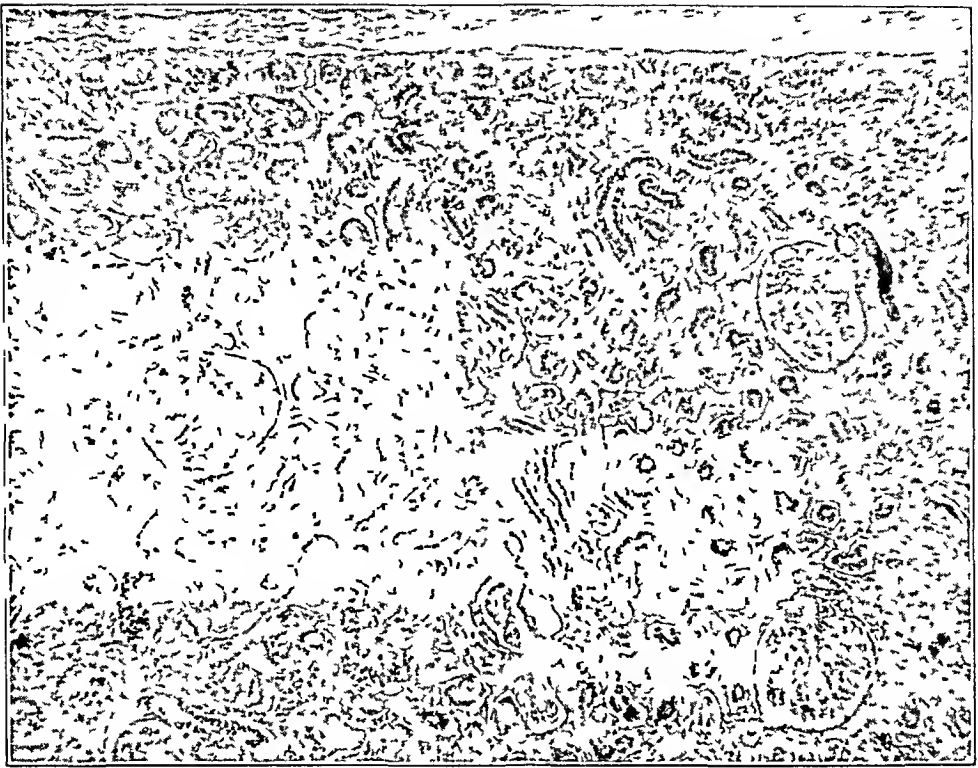


Fig 3—Adjacent areas in the renal cortex. The convoluted tubules on the left are of normal size but exhibit evidence of acute infarction. Those on the right show the fetal character and stromal increase described in the text. The glomeruli in both regions are normal.

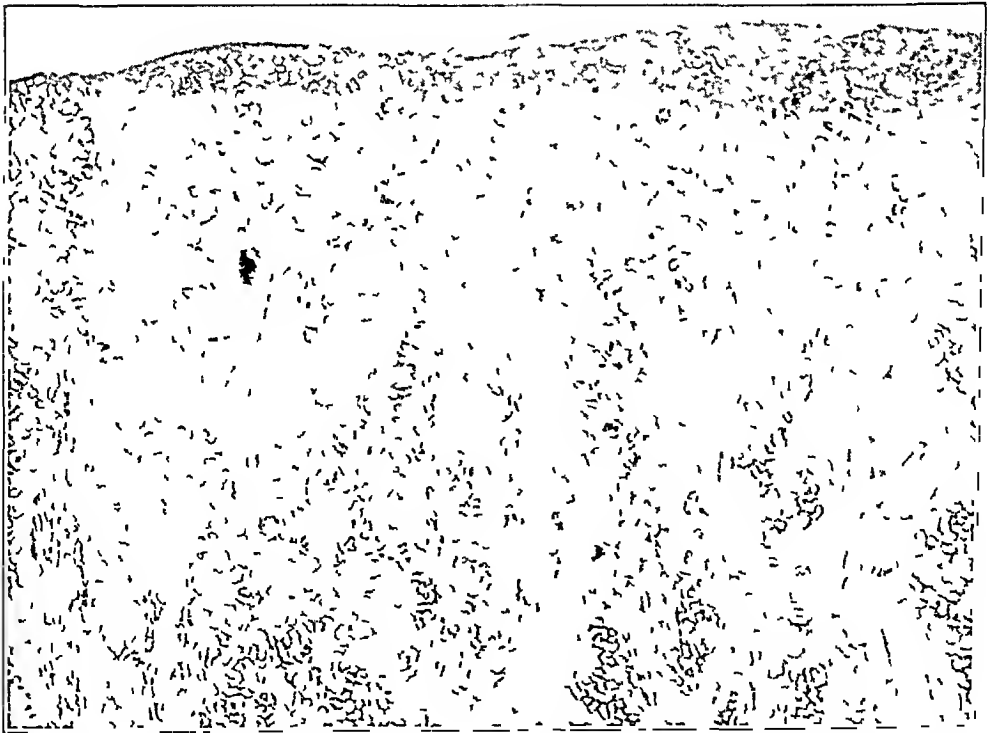


Fig 4—The uniform subendothelial thickening of the course of each interlobular artery is well shown. There is evident focal variation in the convoluted tubules, but the glomerular distribution is not affected.

occasional polymorphonuclear infiltration. The appearance was that of infarction, but there were two striking differences—the glomeruli within these acutely degenerating areas were normal, and there was little significant reaction in the stroma at their periphery, i e, no hemorrhage or fibrosis and but scanty leukocytic infiltration.

The cortical damage was probably associated with the vascular lesions, which were limited to the interlobular arteries supplying the areas of degeneration. Medullary branches of the renal artery appeared to be normal, as were the arcuate

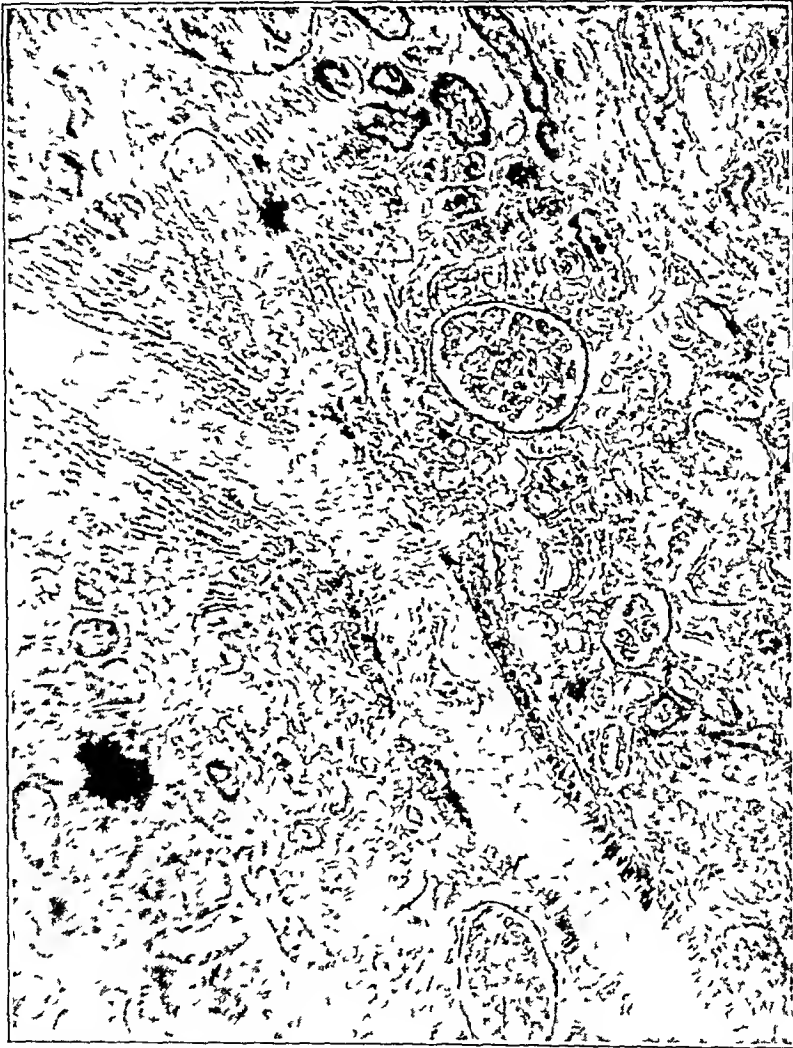


Fig 5—A higher power view of an interlobular artery in longitudinal section. The subendothelial proliferative process extends along its entire course into its major branches, and only a narrow segment of lumen is visible.

arteries, although the latter showed a peculiar intimal thickening in some segments. Radiating interlobular arteries, however, displayed an abrupt change at their points of origin except in regions where the process had begun within the arcuate artery.

Certain sections showed involvement of the entire course of a radiating artery (fig 4) and its larger intralobular branches by a bizarre form of endarteritis. The subintimal substance was infiltrated by a sparsely nucleated, palely basophilic, mucinous material which had the appearance of Wharton's jelly. A few lesions

apparently of earlier origin exhibited frank subintimal fibrosis replacing the mucoid substance. Stains for elastic tissue showed limitation of the lesion to the intima, and in most areas the internal elastic lamina was intact. Several of the older fibrous lesions, however, exhibited reduplication of elastic tissue. Stains for fat showed granules of lipid material within the mucoid substance in the intima. The endarteritic process extended into the larger intralobular arteries, but directly these vessels assumed the caliber of afferent arterioles the intimal changes ceased as abruptly as they had begun.

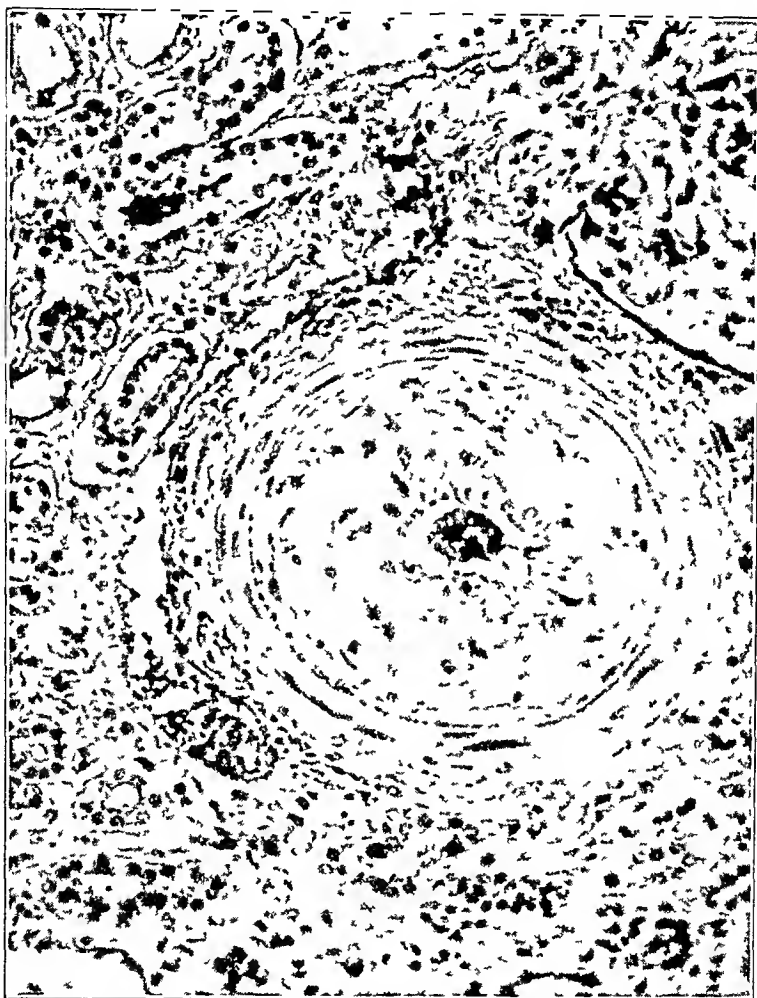


Fig 6—An interlobular artery in cross section. The muscularis is intact, but the mucinous subendothelial process and the narrowing of the lumen are noteworthy.

The lumens were markedly narrowed, often to slitlike orifices, as the result of intimal thickening (figs 5 and 6). The lining endothelial cells were swollen and basophilic but displayed no actual proliferation. Occasional vessels were occluded by hemorrhagic thrombi, with fibrinoid necrosis which was limited to the intima and the inner half of the muscularis. Slight exudation was associated with this necrosis (fig 7), but certain arteries, apparently those previously thrombosed, exhibited complete fibrous organization without recanalization.

**Liver** Uniformly within the central half of all lobules the endothelial lining was widely separated from the underlying cell cords and exhibited fibrinoid thickening. The hepatic cells were shrunken, and immediately surrounding the central vein of each lobule there was a single layer of necrotic parenchymatous cells. The sinusoids contained large numbers of polymorphonuclear cells, although there were relatively few red blood cells. The peripheral half of the lobules exhibited marked and contrasting swelling, with coarse vacuolation in abundance.

**Spleen** The splenic corpuscles were enlarged, and most of them possessed secondary nodules. Although the apparent germinal centers contained a few active-looking stem cells, the predominant cell was a mononuclear phagocyte which was frequently vacuolated. There was slight central fibrosis but no necrosis.

**Lymph Nodes** The normal architecture was preserved, but the stroma and sinuses were filled with large numbers of mononuclear and multinuclear phagocytes.

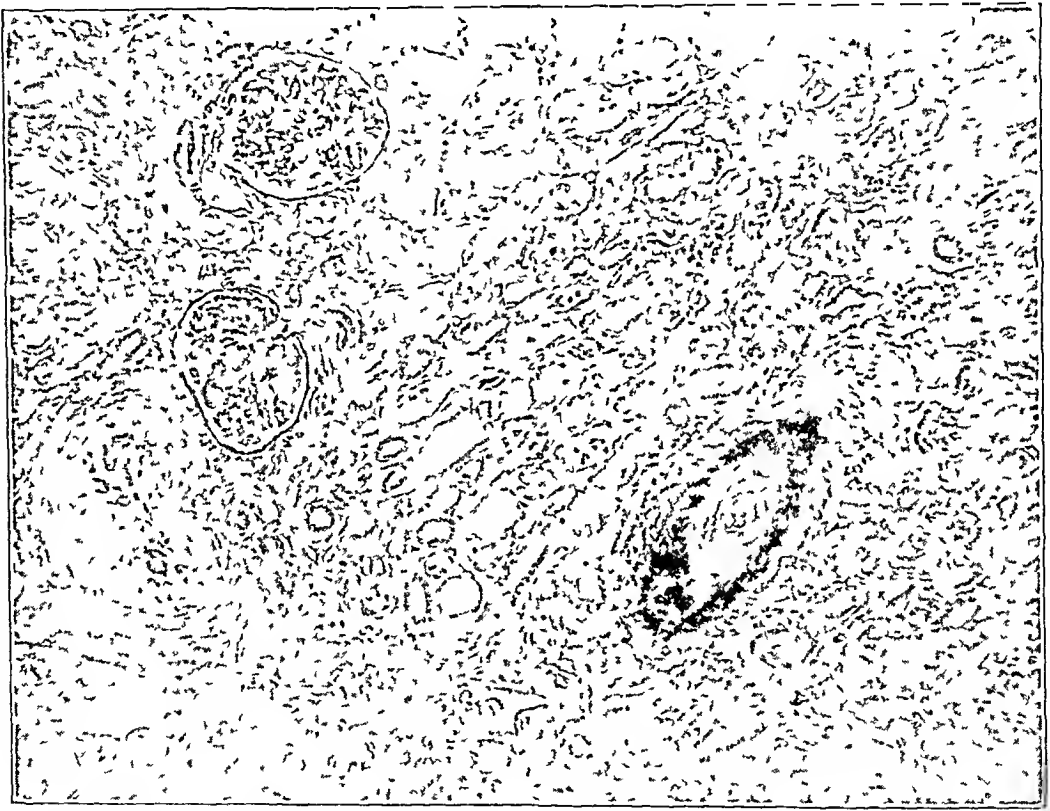


Fig 7—Two adjacent vessels with different lesions. The artery on the left shows the proliferative process without necrosis. The vessel on the right exhibits acute necrosis of the muscularis.

The follicles, as in the spleen, contained well formed central nodules of cells similar to those in the stroma and sinuses.

**Lungs** The alveoli were normal. The nodules observed grossly showed interstitial fibrosis and varying degrees of infiltration with lymphoid cells, monocytes and a few polymorphonuclears. Many alveoli were compressed and lined with cuboidal epithelial-like cells. The pathogenesis of these changes was uncertain.

None of the other organs showed significant parenchymatous abnormalities. All the viscera, however, revealed a slight to moderate grade of vascular change. This consisted of slight subintimal fibrosis, with narrowing of the arterial lumens.

The muscle coats were thickened in places, and there was some perivascular fibrosis. The arterioles frequently showed hyaline intimal thickening. These histologic observations were most evident in the skeletal muscles, the ovaries, the myometrium, the spleen, the myocardium and the region of the fibrotic pulmonary nodules. Serial sections of the pituitary and the parathyroid glands were normal. The bones showed no evidence of active decalcification.

*Anatomic Diagnosis*—The following diagnosis was made: chronic diffuse dermatomyositis with scleroderma, generalized interstitial calcinosis, focal renal tubular infarction, obliterating endarteritis of the interlobular renal arteries, generalized arteriosclerosis and arteriolosclerosis (slight), central lobular necrosis of the liver and follicular hyperplasia of the spleen and the lymph nodes.

*Metabolic Studies*—On her first admission to the metabolic ward the patient was given a constant diet low in sodium for two five day periods. The first five days was used as a preliminary period to allow establishment of approximate nitrogen equilibrium, and no excreta were collected. The food was purchased for five days at a time, and one half of a duplicate day's diet from the second period was weighed, dried and analyzed. The methods employed for analysis of the blood, excreta and diets have been described.<sup>14</sup>

Harrop<sup>15</sup> has shown that when a patient with adrenal insufficiency is given a diet low in salt there may be a significant negative chloride balance. It has been observed in this laboratory<sup>16</sup> and reported by Wilder and his associates<sup>17</sup> that there may be simultaneous retention of potassium. During the five day period of observation of our patient there were a negative chloride balance (tables 1 and 2) of 15 milliequivalents per day and a positive potassium balance of a similar amount. Stool collections were not made during the first period of hospitalization. These data, therefore, do not include excretion of electrolytes in the feces.

During the second period in the hospital, one year later, the patient was given a diet low in calcium with added sodium chloride for three five day periods. A preliminary period was prescribed as before, and data from the second and the third period only are included in the tables. During these periods stool collections were made. This ten day period of study showed certain changes not previously observed. The chloride and the potassium imbalance were confirmed, but the amounts were considerably less than those initially noted. With a high sodium intake the negative balance of this constituent was 35 milliequivalents per day. The total excretion of calcium was about four times that contained in the diet and was about equally divided between the urine and the stool. The total excretion of phosphate was only 12 per cent greater than the intake.

Nitrogen equilibrium was not reached during the second period of observation, in fact, there was a positive balance of 21 per cent. Thus, in terms of nitrogen

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14 Talbott, J. H., Jacobson, B. M., and Oberg, S. A. The Electrolyte Balance in Acute Gout, *J. Clin. Investigation* **14** 411, 1935. Dill, D. B., Talbott, J. H., and Consolazio, W. V. Blood as a Physiochemical System. XII. Man at High Altitudes, *J. Biol. Chem.* **118** 649, 1937.

15 Harrop, G. A., and Weinstein, A. Studies on the Suprarenal Cortex. I. Cortical Suprarenal Insufficiency and the Action of the Cortical Hormone upon the Normal and Suprarenalectomized Dogs, *J. Exper. Med.* **57** 305, 1933.

16 Talbott, J. H. Unpublished data.

17 Wilder, R. M., Kendall, E. C., Snell, A. M., Kepler, E. J., Ryneerson, E. H., and Adams, M. Intake of Potassium, an Important Consideration in Addison's Disease. A Metabolic Study, *Arch. Int. Med.* **59** 367 (March) 1937.

exchange the patient was not suffering from a wasting disease. The concentration of ammonia in the urine was included because it is believed to be an index of renal function. In the presence of severe renal damage, formation or excretion of ammonia by the kidneys may be diminished.<sup>18</sup> There is no evidence from the data on this patient that this function of the kidneys was seriously impaired up to a few weeks before death.

The experimental observations on arterial blood for the year during which the patient was under observation are given in table 3. The cell volume was normal when it was first observed but gradually diminished as death approached. When the oxygen capacity was determined it was below normal but was pro-

TABLE 1—*Fluid Intake and Urinalysis*

Date December 1935	Total Fluid In take, Cc	Vol ume, Cc	Urine							Total Nitro gen, Gm
			Total Fixed Base, mEq	Sodium, mEq	Potas sium, mEq	Cal cium, mEq	Ammo nia, mEq	Chlo ride, mEq	Phos phate, Mg	
14 15	2,230	1,805		91.7	58.1	5.0		95.7	524	6.73
15 16	1,910	1,175		61.3	56.1	5.3		72.7	484	6.92
16 17	2,030	1,520		79.5	61.0	5.2		87.4	531	6.86
17 18	2,030	1,165		54.4	45.7	4.6		61.4	531	6.75
18 19	2,030	1,430		63.9	54.0	5.3		67.5	566	6.82
November 1936										
3- 4	2,680	1,970	261.9	225.7	25.4	8.5	20.3	219.0	185	4.71
4- 5	2,680	1,660	230.0	201.8	19.8	8.3	24.1	201.0	204	4.35
5- 6	2,680	1,630	239.5	204.5	19.3	8.0	22.9	201.0	269	4.14
6- 7	2,680	2,350	325.5	284.8	26.6	9.8	34.1	240.8	329	4.75
7- 8	2,680	1,530	204.3	171.5	21.6	7.5	24.6	177.0	237	4.16
8- 9	2,680	1,700	275.2	233.0	21.3	6.6	25.0	221.0	260	3.88
9 10	2,680	1,870	239.0	206.0	23.0	6.9	39.8	195.5	262	3.93
10-11	2,680	1,200	200.0	174.4	20.0	6.3	46.7	172.5	236	4.20
11-12	2,680	1,790	249.6	225.5	24.9	7.0	62.6	221.5	261	4.44
12 13	2,680	720	106.5	90.4	13.0	4.0	24.3	90.7	173	2.88

TABLE 2—*Summary of Metabolic Data*

	First Admission, 5 Day Period			Second Admission, 10 Day Period			
	Intake	Urinary Excretion	Daily Balance*	Intake	Urinary Excretion	Fecal Excretion	Daily Balance
Sodium, mEq	336	351	+ 7.0	1,823	2,018	173	-35.3
Potassium, mEq	353	275	+15.6	361	215	93	+ 5.3
Calcium, mEq	240	25	+43.0	33	73	96	-14.6
Chloride, mEq	308	385	-15.6	1,947	1,970	48	- 7.1
Phosphate, mg	2,400	2,640	-48.0	3,980	2,420	2,190	-63.0
Total nitrogen, Gm				62	42	7	+ 1.3

\* Balance for intake and urinary output only

portional to the decrease in cell volume. The concentration of sugar in the blood was normal on five determinations.

The acid-base balance of the serum was extremely interesting. On none of the days when it was observed was it normal. The concentration of sodium in the serum on entry was 127.3 milliequivalents per liter, this increased after institution of a diet rich in salt to 138.4 milliequivalents per liter. During the next six months it remained slightly below normal, and after that it decreased progressively as the patient became lax in taking added salt. On September 21 the

18 Peters, J. P., and Van Slyke, D. D. Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins Company, 1932, vol. 1



concentration was 126.8 milliequivalents per liter, the lowest value observed. The patient was again given a high salt diet, and again the concentration of sodium increased. On the day of death it was 137.4 milliequivalents per liter. The concentration of chloride in the serum, on the other hand, was either normal or slightly below normal, and on none of the days when it was observed was it less than 97.4 milliequivalents per liter. In the classic form of Addison's disease<sup>19</sup> the decrease in the chloride content of the serum is quantitatively similar to the decrease in sodium. Although this sequence of events is not invariable, the failure of our patient to conform should have suggested that the chemical changes were not primarily the result of adrenal insufficiency. The concentration of potassium was determined in two specimens of serum and found to be normal.

The concentration of calcium was normal on two determinations and slightly below normal on a third. The concentration of phosphate on two determinations was normal. The concentration of serum protein, on the other hand, was 7.7 Gm

TABLE 3—*Experimental Observations on Arterial Blood and Plasma*

Date	Whole Blood			True Plasma								
	Oxygen Capacity, Vol %	Cell Volume, %	Sugar, Mg per 100 Cc	Total Base, mEq per Liter	Sodium, mEq per Liter	Potassium, mEq per Liter	Calcium, mEq per Liter	Bicarbonate, mEq per Liter	Chloride, mEq per Liter	Phosphate, mEq per Liter	Protein, Gm per 100 Cc	Nonprotein Nitro- gen, Mg per 100 Cc
12/11/1935		39.5	93		127.3				105.7		7.7	52
12/17/1935		39.4	97		132.5				104.1		7.3	36
12/30/1935		38.0	96		138.4			26.2	102.1		7.5	40
1/14/1936		40.7	111		137.1			23.6	101.6		7.9	24
2/21/1936		39.9	103		136.4			25.2	98.9			34
4/ 3/1936	15.1	36.5		146.7	136.8			25.8	102.6		8.4	34
6/12/1936	15.1	37.3			133.8			23.5	98.4		9.3	20
9/21/1936	14.0	32.1		139.2	126.8			25.4	101.3		9.0	
10/14/1936	13.8	31.1		137.9	128.5			25.0	97.4		8.2	20
10/27/1936		32.4		139.4	130.7	3.9	4.0	26.4	97.9	2.1	8.3	20
11/13/1936		31.8		143.3	132.3		5.0	24.2	103.6	2.2	8.3	20
11/30/1936				145.1	137.4	4.8	4.4		100.3		8.4	34

per hundred cubic centimeters on admission, and during the eight months before death it was more than 8.1 Gm. The maximum concentration observed was 9.3 Gm.

Complete data for acid-base balance were not obtained for each specimen of blood. In several samples taken during the last three months of life, however, the sum of the acids was greater than the total base content. Thus, on October 27 the sum of the acids was 146.5 milliequivalents per liter, and the total base content was 139.4 milliequivalents per liter. Two explanations for these unusual observations may be offered. Calculation of base bound by protein, according to Van Slyke and others,<sup>20</sup> may not be applicable to the serum in this case. This

19 Loeb, R. F. Chemical Changes in the Blood in Addison's Disease, *Science* **76** 1932, 1932.

20 Van Slyke, D. D., Hastings, A. B., Hiller, A., and Sendroy, J., Jr. Studies of Gas and Electrolyte Equilibria in Blood. XIV. The Amounts of Alkali Bound by Serum Albumin and Globulin, *J. Biol. Chem.* **79** 769, 1928.

is in agreement with the reports by Gutman and Gutman,<sup>21</sup> who have observed in some serums with an increased concentration of globulin the inapplicability of the formula. Secondly, an increase of the total acid over the total base content is not a unique observation<sup>22</sup> and would possibly be noted in other diseases if this relation were investigated.

The nonprotein nitrogen content of the serum was 52 mg per hundred cubic centimeters on entry and decreased to 24 mg in the following eight weeks. During the second period of hospitalization the concentration of this constituent remained below 22 mg per hundred cubic centimeters until the day of death, when it was 35 mg.

The Wassermann reaction of the blood and spinal fluid as well as the Wassermann reaction of the husband's blood was negative. The colloidal gold curves were probably associated with the increased concentration of globulin in the serum and spinal fluid and were not thought to be indicative of syphilis of the central nervous system.

#### COMMENT

It is believed that a presumptive diagnosis of Addison's disease as well as scleroderma was justified on this patient's admission to the hospital, as most of the criteria were satisfied. There were a history of exposure to tuberculosis, symptoms of weakness and malaise, gastrointestinal disturbances and considerable loss in weight. On physical examination the pigmentation of the skin was typical of the patchy pigmentation seen in certain patients with chronic adrenal insufficiency. Postural hypotension was demonstrated. The concentration of sodium in the serum was 127.3 milliequivalents per liter on entry and increased to 138.4 milliequivalents per liter when a high salt regimen was instituted. The nonprotein nitrogen content was above normal initially and decreased during treatment. A negative chloride balance was observed when the patient was studied in the metabolic ward. The diagnosis of Addison's disease seemed inaccurate, however, as the scleroderma progressed and calcinosis developed. In retrospect, we believe that for a diagnosis of Addison's disease the only important criterion lacking was pigmentation of the mucous membranes. The possibility of partial adrenal insufficiency during the first period of hospitalization, as in the case recorded by MacCallum,<sup>23</sup> appeared to be excluded by the absence of autopsy evidence of previous damage to the glands. MacCallum's patient suffered from acute scleroderma and at autopsy showed adrenal atrophy.

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21 Gutman, A. B., and Gutman, E. B. Relation of Serum Calcium to Serum Albumin and Globulin, *J. Clin. Investigation* **16** 903, 1937.

22 Gutman, A. B., Gutman, E. B., Jillson, R., and Williams, R. D. Acid-Base Equilibria of the Blood in Diseases Associated with Hyperglobulinemia, with Special Reference to Lymphogranuloma Inguinale and Multiple Myeloma, *J. Clin. Investigation* **15** 475, 1936.

23 MacCallum, W. G. Acute Diffuse Scleroderma, *Tr. A. Am. Physicians* **41** 190, 1926.

It is frequently difficult clinically to differentiate scleroderma and dermatomyositis, and in consideration of the observations at autopsy such a differentiation is believed to be futile in this instance. Raynaud's disease and sclerodactylia may precede or be associated with scleroderma. This patient had neither the acute symptoms of the first condition nor the localized decalcification characteristic of the second. Generalized decalcification of the skeleton was seen at roentgen examination, but this was not confirmed by the histologic studies.

The possibility that this disturbance might be related to a primary disorder of calcium and phosphorus metabolism, such as *calcinosis universalis*,<sup>24</sup> cannot be excluded. The concentrations of these constituents in the serum were normal at two examinations, however, and at the first entry a normal amount of calcium was excreted in the urine. During the second period in the hospital there was a moderate negative balance. Thyroid dyscrasia has been implicated in the pathogenesis of scleroderma by many observers.<sup>25</sup> There was no histologic or metabolic evidence of myxedema in this case, however, and determination of the basal metabolic rate showed no evidence of hyperthyroidism.

We shall discuss the anatomic observations with respect to (1) changes related to the muscular dyscrasia and (2) the changes in the kidneys. The distribution and variability of the histologic changes in the muscle were consistent with a diagnosis of idiopathic nonsuppurative myositis or dermatomyositis.<sup>26</sup> It seems probable that the abnormalities in the adjoining vessels were secondary to the surrounding inflammatory reaction. The perineural lymphocytic infiltration evidently had a similar pathogenesis. There was no histologic evidence to incriminate the central or the peripheral nervous system as a causative factor. Microorganisms such as have been described by Boothby<sup>27</sup> as present in the muscles of patients with myasthenia gravis were not demonstrated.

The inflammatory and reparative processes in the subcutaneous and the deeper connective tissue planes are also believed to be the result of

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24 Bauer, W. *Calcinosis*, in *The Practitioners Library of Medicine and Surgery*, New York, D. Appleton-Century Company, Inc., 1938, vol. 13. Bauer, W., Marble, A., and Bennett, G. A. *Further Studies in Calcification of Subcutaneous Tissue ("Calcinosis Universalis") in a Child*, *Am J M Sc* **182**: 237, 1931.

25 Durham, R. H. *Scleroderma and Calcinosis*, *Arch Int Med* **42**: 467 (Oct.) 1928. Castle, W. F. *The Endocrine Causation of Scleroderma, Including Morphea*, *Brit J Dermat* **35**: 255, 1923.

26 (a) Langmead, F. S. *The Relationship Between Certain Rare Diseases: Generalized Scleroderma, Calcinosis, Dermatomyositis, and Myositis Fibrosa*, *Arch Pediat* **40**: 112, 1923. (b) Gans, O. *Histologie der Hautkrankheiten*, Berlin, Julius Springer, 1925, vol. 1, p. 147. (c) Karlmark, E. *Zur Pathologie der Polymyositis*, *Acta med Scandinav* **72**: 59, 1929.

27 Boothby, W. M. *Myasthenia Gravis*, *Tr A Am Physicians* **51**: 188, 1936.

adjacent muscular destruction<sup>28</sup> It is recognized that calcification frequently follows inflammation and degeneration of adipose tissue<sup>29</sup> With so diffuse an inflammatory background as this, widespread calcinosis may be an anticipated sequela Similarly, the scleroderma may possibly be attributed to an extension of the underlying inflammatory process and its effect on the vascular and nervous supply of the skin<sup>30</sup> The relation of the resultant dermatomyositis to true scleroderma is uncertain,<sup>31</sup> but the overlapping of the histopathologic changes associated with these conditions suggests a common cause for both<sup>26a</sup>

If it is granted that the dermatomyositis has an inflammatory pathogenesis, any attempt to correlate the condition with the degenerative lesion in the kidneys is relatively unsuccessful The lack of similarity between the vascular changes in the muscles and the bizarre arterial lesions in the kidneys is obvious It is possible that the vascular lesions in the kidneys were the result of mild but continuous irritation Substances liberated by muscular degeneration, in combination with the disordered cutaneous excretory power, may have been the source of this irritation Scriver and Oertel<sup>32</sup> have recorded observations which suggest a specific susceptibility of the renal interlobular arteries to noxious stimuli They have reported acute bilateral necrosis of the renal cortex in occasional cases of late toxemia of pregnancy There is little evidence to suggest that our patient had severe toxemia of pregnancy, although her physician found albumin in the urine before delivery and her symptoms began six weeks post partum In kidneys with bilateral cortical necrosis the lesions are generally acute and in the same stage of development<sup>33</sup> Nevertheless, the distribution of the process is similar to that observed in this patient, and the kidneys grossly resembled those described in the literature<sup>34</sup>

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28 Klingman, W O Dermatoneuromyositis Resulting in Scleroderma, *Arch Neurol & Psychiat* **24** 1187 (Dec) 1930

29 Wells, H G Chemical Pathology, ed 5, Philadelphia, W B Saunders Company, 1925, p 493

30 Rake, G On the Pathology and Pathogenesis of Scleroderma, *Bull Johns Hopkins Hosp* **48** 212, 1931

31 Klingman<sup>28</sup> Wells<sup>29</sup>

32 Scriver, W de M, and Oertel, H Necrotic Sequestration of the Kidneys in Pregnancy (Symmetrical Cortical Necrosis) A Clinical and Anatomic-Pathogenetic Study, *J Path & Bact* **33** 1071, 1930

33 De Navasquez, S The Histology and Pathogenesis of Bilateral Cortical Necrosis of the Kidney in Pregnancy, *J Path & Bact* **41** 385, 1935

34 (a) Jardine, R, and Teacher, J H Two Cases of Symmetrical Necrosis of the Cortex of the Kidneys Associated with Puerperal Eclampsia and Suppression of Urine, *J Path & Bact* **15** 137, 1911 (b) Bamforth, J A Case of Symmetrical Cortical Necrosis of the Kidneys Occurring in an Adult Man, *ibid* **26** 41, 1923 (c) Bradford, J R, and Lawrence, T W P Endarteritis of the Renal Arteries Causing Necrosis of the Entire Cortex of Both Kidneys, *ibid* **5** 195, 1898

In view of the macroscopic resemblance it is of interest that in both conditions the vascular lesions are limited to the interlobular arteries. Although intimal thickening is not regularly observed in cases of acute necrosis, several cases reported in the literature,<sup>35</sup> as well as an unreported case from this hospital have included evidence of chronic fibrous thickening of the intima in addition to hyaline thrombosis. It is believed that in this case, only the massive thrombosis accompanying puerperal cortical necrosis is lacking to complete the histologic picture.

The arterial lesion in this case was unusual in other respects. It was confined to the intima, it involved uniformly the postarcuate and the prearteriolar segments of the renal arterial tree and it had an unusual mesenchymal appearance (fig 6). The last mentioned phenomenon has been termed mucoid endarteritis by Jores<sup>36</sup> and is probably an early manifestation of a subintimal process terminating in fibrosis. Medial changes were limited to those vessels in which thrombosis occurred. In these areas partial necrosis was present, but the involvement rarely extended beyond the central portion of the muscular coat. Even in the absence of an occlusive process (figs 4 to 6) the arterial lumens were sufficiently stenosed to produce ischemia.

The selective tubular degeneration was associated with the diminution in vascular supply, and the foci of actual cortical necrosis occurred only in areas where the thrombosis had occluded the nutrient vessels. MacCallum<sup>37</sup> has shown that each cortical artery terminates in a glomerular tuft from which an efferent arteriole transmits blood to a plexus surrounding a convoluted tubule. A descending medullary vessel reforms from this plexus and in turn joins an anastomotic network in the medullary substance. If this is so it is possible that the glomeruli suffer less from the ischemia than the other elements of the nephron. Relative glomerular resistance to oxygen lack has been demonstrated by Fahr,<sup>38</sup> Maatz<sup>12</sup> and Zeckwer.<sup>39</sup> It is believed that the absence of significant changes in the collecting tubules may be related to the rich capillary anastomoses in the medulla.

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35 Jardine and Teacher<sup>34a</sup> Bradford and Lawrence<sup>34c</sup>

36 Jores, L. Arterien Produktive Endarteritis, in Henke, F., and Lubarsch, O. Handbuch speziellen pathologischen Anatomie und Histologie, Berlin, 1924, Julius Springer, vol 2, p 644

37 MacCallum, D. B. The Arterial Blood Supply of the Mammalian Kidney, *Am J Anat* **38** 153, 1926

38 Fahr, T. Kreislaufstörungen in der Niere, in Henke, F., and Lubarsch, O. Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1925, vol 6, pt 1, p 148

39 Zeckwer, I. T. The Persistence of the Glomerular Circulation Following Occlusion of the Renal Vein of One Kidney in the Cat, *Am J Path* **2** 57, 1926

The renal process may therefore be interpreted as incomplete bilateral cortical necrosis similar in many respects to that reported by Branson<sup>40</sup> and by Mallory<sup>13</sup>

It is not believed, however, that the patient died of renal insufficiency. It is a fact that three weeks before death the ability to concentrate solids was lost and that excretion of phenolsulfonphthalein was below normal. Opposed to these two clinical tests are the following points: (1) lack of elevation of the concentration of nonprotein nitrogen or of phosphate in the serum, (2) lack of evidence of acidosis as determined by the concentration of serum bicarbonate, (3) lack of diminution of ammonia excretion and (4) adequate excretion of fluid and salts. Nor is there evidence that this patient was suffering from chronic nephritis of long duration, which has been known to lead to "metastatic" calcification with hyperplasia of the parathyroids.

Both Maatz<sup>12</sup> and MacNider<sup>41</sup> have shown that renal tubules severely injured by ischemia or by noxious substances may regenerate with undifferentiated epithelium. MacNider has shown that the functional effectiveness of such epithelium is appreciably impaired. Since it is recognized that the convoluted tubules are intimately associated with salt exchange,<sup>42</sup> it is possible that the negative salt balance in our case was caused by these morphologic changes.<sup>43</sup>

The degenerative changes noted in the liver and lymphoid follicles must have resulted from relatively severe systemic toxemia. If these changes are considered in conjunction with the muscular and renal lesions, a common pathogenic agent may be assumed. Furthermore, diffuse vascular lesions such as the patient showed are not infrequently encountered in elderly persons and in persons with hypertension. This patient, however, was only 26 years of age and had no elevation of blood pressure. The arterial changes, though individually insignificant, when viewed as a whole link themselves with the other focal processes and assume greater importance as a manifestation of a systematic disease, the precipitating cause of which remains obscure.

#### SUMMARY

Studies of a patient with dermatomyositis, scleroderma and calcinosis are reported. On entry the clinical diagnosis was Addison's

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40 Branson, W. P. S. Obliterative Arteritis, *Tr. Path. Soc. London* **56**: 212, 1905.

41 MacNider, W. de B. A Study of Renal Function and the Associated Disturbance in the Acid-Base Equilibrium of the Blood in Certain Experimental and Naturally Acquired Nephropathies, *Arch. Int. Med.* **26**: 1 (July) 1920.

42 Smith, H. W. *The Physiology of the Kidney*, New York, Oxford University Press, 1937.

43 Pohl, J. Ueber subakute Nephritis, *Arch. f. exper. Path. u. Pharmacol.* **67**: 233, 1911.

disease This was apparently substantiated by a history of weakness, gastrointestinal disturbances, loss of weight and cutaneous pigmentation On physical examination there was postural hypotension Metabolic studies showed a negative sodium and a negative chloride balance In the blood there was an increased concentration of serum protein, a decreased concentration of total bases and an excess of determined acid over determined base With a high intake of sodium chloride there was a transient regression of symptoms

At necropsy the adrenal glands were normal There was severe dermatomyositis associated with deposition of calcium in the connective tissue planes A peculiar form of mucoid endarteritis limited to the interlobular arteries of the kidneys was associated with ischemic changes in the renal cortex The similarity of these changes to those observed in bilateral renal cortical necrosis of pregnancy was noted The initiating factor of the visceral and diffuse muscular lesions was not evident

NOTE—Since the submission of this paper for publication a report<sup>44</sup> has appeared of a case of scleroderma with generalized visceral and cutaneous vascular changes Although the arterial lesions in the two cases exhibited a degree of similarity, there was considerable difference in the distribution, variation and apparent severity of the process Myositis, calcinosis and focal renal infarction were not recorded Moreover, necropsy revealed extensive glandular tuberculosis with terminal miliary spread There were also Aschoff nodules in the myocardium Metabolic studies were not performed

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44 Masugi, M, and Ya, S Die diffuse Sklerodermie und ihre Gefassveränderung, *Virchows Arch f path Anat* **302** 39, 1938

# RELATION OF HYPERTHYROIDISM TO HYPERTENSION

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OMAHA

Since hyperthyroidism is a general disease in which one of the most fundamental physiologic processes of the body is abnormally accelerated, it influences organic functions generally. The changes in vascular tonus and the increase in cardiac output and in velocity of blood flow are usually reflected in some alterations of blood pressure. In the characteristic case, the systolic pressure shows a slight to moderate elevation while the diastolic pressure remains relatively unchanged or is slightly lowered, resulting in an increase of pulse pressure. That these changes represent physiologic responses to the disease is indicated by the fact that the pressures assume their previous normal levels with remission of the metabolic rate to a normal basal level.

There are, however, cases in which the systolic pressure is higher than that occurring in the kind of case just indicated or in which both the systolic and the diastolic pressure are considerably elevated. In these cases the pressures either are uninfluenced by remission of the hyperthyroidism or fail to return completely to normal levels with this remission. To investigate such cases, the following analyses were compiled. From these records it is possible to distinguish two types of cases, which will be discussed subsequently.

## ANALYSES OF CASES

The data which follow were obtained from 265 cases of hyperthyroidism. The patients were 211 women and 54 men, and all were treated by subtotal thyroidectomy. For the entire group the average age was 36 years, the duration of toxic symptoms thirteen months and the basal metabolic rate  $+43.4$  per cent. The preoperative blood pressure averaged 140 mm of mercury systolic and 76.5 diastolic. The systolic pressure exceeded 150 mm in 80 cases, or 30 per cent of the series, 160 mm in 50, or 18.9 per cent, and 200 mm in 9, or 3.4 per cent. These observations are shown in greater detail in table 1. This table also shows that in general the patients with higher pressure were older and had had thyrotoxic symptoms for a longer time.

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Assuming that a systolic pressure above 145 mm of mercury is definitely abnormal, I attempted to make follow-up observations in all cases in which the systolic pressure was above this level and the post-operative period exceeded twelve months. Records were obtained in 38, or approximately one half, of the cases, and a comparison of the preoperative and postoperative blood pressure levels is shown in tables 2 and 3.

The 38 cases have been divided into two groups: (1) those in which the preoperative systolic pressure was between 145 and 170 mm of mercury, and (2) those in which it was 170 mm or more.

In the first group there were 26 cases. In 19, or 73 per cent, of these the systolic pressure one year or more after operation showed some reduction from the preoperative level, and in 14 of the 19, or

TABLE 1—*Data Obtained from Analyses of Two Hundred and Sixty-Five Cases of Hyperthyroidism*

Classification	Number of Patients	Per centage of Total Cases	Averages					Duration of Toxic Symptoms, Mo
			Sys tolic Pres sure	Dias tolic Pres sure	Pulse Pres sure	Basal Metabolic Rate, %	Age of Patient	
Total cases studied	265		140	76.5	63	+43.4	36	18
Systolic pressure over 150	80	30						
Systolic pressure over 160	50	18.9	177	90	90.5	+43.5	41.5	20
Diastolic pressure over 90	50	18.9						
Systolic and diastolic pressure over 150/90	37	14						
Systolic and diastolic pressure over 160/100	14	5.2	193	110.7		+38	45.5	23.5
Systolic pressure over 200	9	3.4	226	103	110	+37	45.5	25

53 per cent, of the group there was considerable reduction, in 9 cases the pressure became normal. There was a reduction of diastolic pressure in 12 cases. Systolic pressure increased in 4 cases and diastolic pressure in 9 cases. There was no change of pressure in 2 cases.

In the second group there were 12 cases (table 3). In 5 of these, or 45.4 per cent, reductions of both the systolic and the diastolic pressure had followed thyroidectomy and had been maintained for periods of one to five years. In 3 of the 5 cases the pressure was nearly normal. In 3 cases there was an increase of pressure, in 2 of them an extreme increase. In 2 cases there was little or no change of pressure.

Combining the figures from the two groups shows that in 19 cases the blood pressure was uninfluenced by relief of hyperthyroidism and either remained unchanged or continued to increase. In 19, or an equal number of cases, however, the blood pressure was appreciably reduced after thyroidectomy, and in 11 it became relatively normal or nearly normal.

TABLE 2—Analysis of 26 Cases of Hyperthyroidism in Which the Patient Had a Preoperative Systolic Pressure Between 145 and 170

Age	Sex	Duration of Toxæmic Symptoms	Basal Metabolic Rate, %	Pathologic Condition	Preoperative Pressure		Pressure 1 Year or More After Operation		Reduction, Mm		Increase, Mm	
					Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic
45	F	1 yr	+37	Adenomatous hyperplasia	160	72	132	68	28	4		
18	F	1 yr	+55	Hyperplasia	155	100	119	83	36	17		
39	F	4 mo	+34	Carcinoma	160	100	122	78	38	22		
56	F	2 mo	+49	Adenomatous hyperplasia	166	66	150	90	16			24
32	F	3 yr	+46	Adenomatous hyperplasia	160	106	115	70	45	36		
35	F	4 yr	+75	Hyperplasia	150	95	130	70	20	25		
18	F	6 mo	+18	Hyperplasia	165	90	124	72	41	18		
22	F	4 yr	+59	Adenomatous hyperplasia	160	80	140	80	20	0		
40	F	3 mo	+23	Adenomatous hyperplasia	160	90	163	100			8	10
38	F	4 yr	+23	Adenoma	168	110	182	120			14	20
21	F	10 mo	+63	Hyperplasia	130	80	140	90	10			10
37	F	2 yr	+17		145	100	180	100			35	0
62	F	5 mo	+91	Hyperplasia	150	70	150	68				
46	F	3 yr	+23	Hyperplasia	150	90	126	82	24	8		
45	F		+41	Hyperplasia	155	80	126	80	29	0		
49	F	5 yr	+54	Hyperplasia	156	70	170	90				20
33	M	2 mo	+36	Hyperplasia	150	70	146	82	4		14	12
57	F	1 yr	+33	Adenomatous hyperplasia	153	78	140	100	18			22
24	F	3 yr	+37	Adenomatous hyperplasia	155	72	132	86	23			14
47	M	6 mo	+54	Hyperplasia	150	90	140	75	10	15		
35	F	2 yr	+43	Hyperplasia	145	94	130	80	14	14		
22	F	2 yr	+52	Hyperplasia	152	82	125	70	27	12		
34	F	3 yr	+26	Adenomatous hyperplasia	155	75	155	94			0	19
30	F	3 mo	+54	Hyperplasia	150	80	120	73	30	7		
56	M	3 yr	+29	Adenomatous hyperplasia	150	80	150	80	0	0		
25	M	4 yr	+46	Hyperplasia	150	90	123	84	22	6		

TABLE 3—Analysis of 12 Cases of Hyperthyroidism with Hypertension in Which the Patient Had a Systolic Pressure of 170 or More

Age	Sex	Duration of Toxic Symptoms	Basal Metabolic Rate, %	Pathologic Condition	Preoperative Pressure		Pressure 1 Year or More After Operation		Reduction, Mm		Increase, Mm	
					Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic
62	F	2 yr	+28	Adenomatous hyperplasia	250	120	180	80	70	40		
32	F	7 yr	+78	Hyperplasia	200	100	120	72	80	28		
47	F	18 mo	+48	Cystic adenoma	182	100	142	80	40	20		
23*	F	1 yr	+63	Hyperplasia	178	80	65	50	113	30		
41	F	1 yr	+31	Adenomatous hyperplasia	172	90	230	124			53	84
48	F	1 yr	+75	Hyperplasia	170	90	161	90	6	0		
26	F	6 mo	+25	Hyperplasia	170	90	130	85	40	5		
48	F	2 yr	+51	Adenomatous hyperplasia	170	90	210	100			40	10
56	M	2 yr	+55	Adenomatous hyperplasia	170	90	180	90			10	0
58	M	2 yr	+48	Adenomatous hyperplasia	180	110	130	90	50	20		
23	M	6 mo	+51	Hyperplasia	170	80	170	88			0	8
48	F	9½ mo	+60	Adenomatous hyperplasia	230	140	210	140	20	0		

\* Since this patient also had diabetes mellitus and Simmond's disease her case was not included in the statistical calculations

## COMMENT

As stated previously and as indicated by the data compiled in tables 2 and 3, cases of hyperthyroidism with hypertension which exceeds that considered physiologic can be classified as of two types

1 A type in which hyperthyroidism and an established hypertension coexist incidentally in the same person as separate, unrelated entities. Usually the hypertension is essential in type, although its severity apparently is increased by the thyrotoxic state, and some improvement may follow release from hyperthyroidism. Despite symptomatic improvement, however, the blood pressure, both systolic and diastolic, remains high and usually is not significantly lowered, and the disease continues to progress.

2 A type in which relief of hyperthyroidism by subtotal thyroidectomy causes both the systolic and the diastolic pressure to recede promptly to a much lower, normal or nearly normal level, at which it remains or from which after a period of many months it again gradually ascends. This response suggests that thyrotoxicosis in these cases either is directly responsible for the hypertension or, more likely, precipitates or exaggerates a latent vascular disorder. It is conceivable that an inelastic or restricted vascular bed, capable of receiving the normal cardiac output without appreciable elevation of blood pressure, would be unable to receive the increased output incident to hyperthyroidism without a sharp rise in the propelling force. Conversely, with lessening of the output by remission of hyperthyroidism the pressure required to propel the blood is diminished. In other words this hypothesis assumes the existence of arteriolar pathologic changes which are insufficient to increase appreciably the resistance to a normal volume of blood flow but which are sufficient to prevent normal expansion as the load is increased.

This hypothesis finds support in the observations which follow. In 5 cases (3 of the group in table 3 and 2 private cases not included in the present series) determinations were made of the response of blood pressure to exercise and to the cold pressor test of Hines and Brown.<sup>1</sup> These determinations are shown in table 4. In all cases large reductions of blood pressure had developed and been sustained after subtotal thyroidectomy.

After the basal level of blood pressure had been obtained, each patient was given sufficient exercise to increase the pulse rate appreciably (from 16 to 40 beats per minute), and the blood pressure was determined immediately afterward and at subsequent intervals of sixty

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1 Hines, E. A., and Brown, G. E. The Hereditary Factor in the Reaction of Blood Pressure to a Standard Stimulus (Cold), *Proc. Staff Meet. Mayo Clin* 10: 371 (May 29) 1935.

seconds. In each instance the pressure rose to the approximate preoperative resting level. Moreover, these levels were sustained abnormally long and receded abnormally slowly. Thus the response of blood pressure to the increased cardiac output incident to exercise was approximately the same as that recorded preoperatively during the thyrotoxic state.

Each patient was then subjected to the cold pressor test described by Hines and Brown. In accordance with their technic the lowest or basal level of blood pressure was obtained with the subject resting supine for thirty minutes or longer. With the blood pressure cuff in place on one arm, the opposite hand was immersed in ice water (4 C) to a point just above the wrist for sixty seconds, and readings of blood pressure were made thirty and sixty seconds after the beginning of immersion. Within thirty seconds the pressure again mounted to

TABLE 4—*Effect of Exercise and of the Cold Pressor Test on the Blood Pressure of Patients Who Had Undergone Subtotal Thyroidectomy*

Case	Age of Patient	Preoperative Basal Meta-bolic Rate	Postoperative Pulse Rate (Resting)	Blood Pressure				Pulse Rate	
				Pre-operative	Post-operative	After Exercise	After Immersion of Hand	After Exercise	After Immersion of Hand
1	47	43	76	182/100	142/ 80	195/ 95	185/105	104	82
2	58	48	84	180/110	130/ 90	190/100	185/105	110	92
3	62	28	68	250/120	180/ 80	230/110	230/110	100	74
4	60	62	82	210/110	150/105	220/112	218/110	98	80
5	56	58	72	190/115	150/108	190/120	200/124	112	72

approximately the same level which followed exercise. In the light of the studies of Hines and Brown, the reaction of the blood pressure in these patients was excessive and abnormal, as is that in all subjects afflicted with essential hypertension. The studies of these investigators showed that in addition to the persons with hypertension there is a group of persons who do not have hypertension but do give excessive reactions to the cold pressor test. Persons in this group they designated "hyperreacting normals," and they stated the belief that this excessive reaction indicates a latent quality and a likelihood of subsequent development of hypertension. On this basis it may be reasoned that my patients had potential if not real essential hypertension and that the latent factor had been precipitated or exaggerated by thyrotoxicosis.

It is interesting that in each of these 5 cases there was a familial history of hypertension.

#### CONCLUSIONS

1. As a physiologic response to hyperthyroidism, the systolic blood pressure is usually slightly or moderately elevated. It recedes to the normal level with relief of hyperthyroidism.

2 In a series of 265 cases which I studied, hyperthyroidism was associated with true essential hypertension in approximately 8 per cent and with elevations of the systolic pressure above the physiologic level (above 150 mm of mercury) in 30 per cent. On the basis of changes of blood pressure following relief of hyperthyroidism, two types of cases are discernible: (1) cases with fixed or established essential hypertension, in which the blood pressure and the course of the vascular disease are not significantly influenced by relief of hyperthyroidism, and (2) cases with latent or labile essential hypertension, in which the blood pressure shows considerable reduction after relief of hyperthyroidism or approaches a normal level and maintains this level for a long period. In some cases of the second type the pressure is observed subsequently to ascend. In these cases there is excessive response in blood pressure to exercise and to the cold pressor test of Hines and Brown. It is suggested that the relation of hyperthyroidism to hypertension in these cases is provocative, that hyperthyroidism merely precipitates or exaggerates hypertension which is latent.

It is further suggested that in both types there is arteriolar disease, differing only in degree. In the first type the disease is more advanced, rendering the vascular bed inadequate for even a normal volume of blood flow. In the second type the disease may be designated as pre-tensive hypertension, which progresses to the condition of the first type with the advance of time.

# CHRONIC CONSTRICTIVE PERICARDITIS

## DYNAMICS OF THE CIRCULATION AND RESULTS OF SURGICAL TREATMENT

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Chronic constrictive pericarditis has received increasing attention in this country in the last ten years. White,<sup>1</sup> in 1935, brought together an excellent historic résumé of Pick's syndrome,<sup>2</sup> analyzed the clinical manifestations and recorded the experience which he and Churchill had had with surgical treatment—pericardiectomy. This treatment has been pursued most extensively in this country by Churchill and White,<sup>3</sup> Beck,<sup>4</sup> Blalock and Burwell<sup>5</sup> and us. The syndrome does not appear to be as uncommon as was formerly thought to be the case. The recognition of chronic constrictive pericarditis is important, since it is a cardiac lesion which lends itself to surgical treatment. We have observed 9 patients in the last two and one-half years. Since one group of workers do not have the opportunity to see large numbers of these patients in a short time, we are recording our investigations of the circulation in the

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An abstract of these studies was read before the Association of American Physicians, Atlantic City, N. J., May 5, 1937.

Drs. John E. Deitrick, Norman F. Crane, Robert F. Watson and Charles H. Wheeler assisted in the studies of the circulation.

From the Department of Medicine and the Department of Surgery of the New York Hospital and Cornell University Medical College.

1 White, P. D. Chronic Constrictive Pericarditis (Pick's Disease) Treated by Pericardial Resection, *Lancet* **2** 539 and 597, 1935.

2 Pick, F. Ueber chronische, unter dem Bilde der Lebercirrhose verlaufende Pericarditis (pericarditische Pseudolebercirrhose), nebst Bemerkungen ueber die Zuckergussleber (Curschmann), *Ztschr. f. klin. Med.* **29** 385, 1896.

3 Churchill, E. D. Pericardial Resection in Chronic Constrictive Pericarditis, *Ann. Surg.* **104** 516, 1936. White<sup>1</sup>

4 Beck, C. S., and Griswold, R. A. Pericardiectomy in the Treatment of the Pick Syndrome. Experimental and Clinical Observations, *Arch. Surg.* **21** 1064 (Dec., pt. 2) 1930. Beck, C. S., and Cushing, E. H. Circulatory Stasis of Intrapericardial Origin. The Clinical and Surgical Aspects of the Pick Syndrome, *J. A. M. A.* **102** 1543 (May 12) 1934.

5 Burwell, C. S., and Flickinger, D. Obstructing Pericarditis. Effect of Resection of the Pericardium on the Circulation of a Patient with Concretio Cordis, *Arch. Int. Med.* **56** 250 (Aug.) 1935.

presence of this syndrome together with our experience with the surgical treatment of 7 patients<sup>6</sup>. Clinical observations and studies of the circulation have been made in 9 cases. Resection of part of the pericardium was instituted in 7 of these cases and observations were made both before and after operation.

#### PLAN OF OBSERVATIONS

The patient was admitted to the hospital and remained in bed. The dietary intake of salt was limited to 2 Gm daily and the fluid intake to 1,200 cc. A diet high in protein was given.

Measurements of the circulation were made shortly after the patient was admitted to the hospital, before diuretics were given. By means of medical treatment and drugs, the mobilization of fluids was then encouraged. When the patient had attained his best state, measurements of the circulation were repeated, then pericardial resection was done. At a time during convalescence when the patient was able to cooperate, observations were repeated and as frequently thereafter as changes in the clinical state were apparent. The patient was free from excess fluid on discharge to the outpatient clinic, from which he was readmitted to the hospital for repetition of the studies.

All observations were made in the morning while the patient was in a basal metabolic state. The cardiac output was estimated by the acetylene method, three samples of gas being taken, as first recommended by Grollman<sup>7</sup> and as further elaborated by Grollman, Friedman, Clark and Harrison<sup>8</sup>. During this measurement the patient sat in a steamer chair (at an angle of 135 degrees), having been trained beforehand to carry out the procedures. While he was at rest, the cardiac rate was counted at intervals of five minutes for one-half hour, at the end of this time the mixture of acetylene, air and oxygen was rebreathed. Three samples of gas were taken during each period of rebreathing for estimation of the arterio-venous oxygen difference. The first sample was obtained after the patient had taken ten to twelve breaths in twenty seconds, the second after two to three more breaths and the third after two to three additional breaths. All three samples were usually obtained before the end of thirty seconds. Samples were taken during expiration. Two or three periods of rebreathing were carried out at each measurement. Shortly afterward the oxygen consumption was measured with a Benedict-Roth spirometer. The vital capacity was measured, and the height and weight were recorded. An electrocardiogram was taken, the arm to tongue circulation time recorded, the venous pressure estimated and the blood pressure measured. Finally a roentgenogram of the heart was made at a distance of 2 meters. Sufficient time was allowed between each procedure for restoration of the basal metabolic state.

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<sup>6</sup> Pericardial resection was carried out in these cases by one of us (Dr Heuer).

<sup>7</sup> Grollman A. *The Cardiac Output of Man in Health and Disease*. Springfield, Ill, Charles C Thomas, Publisher, 1932, p. 73.

<sup>8</sup> Grollman, A., Friedman, B., Clark, G., and Harrison, T. R. *Studies of Congestive Heart Failure. XXIII. A Critical Study of Methods for Determining the Cardiac Output in Patients with Cardiac Disease*, *J. Clin. Investigation* 12: 751, 1933.



The arm to tongue circulation time was estimated by the use of decholin, the patient lying quietly in the supine position <sup>9</sup>

The venous pressure was measured by the direct method,<sup>10</sup> a large antecubital vein being used and the arm being placed on a level with the right auricle. Normal pressures recorded with this apparatus range from 4 to 10 cm of saline solution. The antecubital vein of one arm was reserved for the injection of decholin and that of the other arm for the measurement of venous pressure. In subsequent measurements the vein was entered at the site first punctured.

Roentgenograms of the heart were taken during full inspiration, at a distance of 2 meters,<sup>11</sup> with the patient standing. Measurements of the cardiac area were carried out by the technic of Levy,<sup>12</sup> and estimations of volume were made as recommended by Bardeen.<sup>13</sup> Special exposures, anteroposterior as well as lateral, were taken for the detection of calcification. Examination under the fluoroscope was also carried out. Infra-red photographs were taken to record the state of the peripheral veins. The patient assumed as nearly as possible exactly the same position for each observation.

#### RESULTS OF STUDIES OF CIRCULATION

In all but 1 case (case 6) the measurements of the circulation followed a similar pattern.

Before operation the arteriovenous oxygen difference was increased (range, 71.5 to 88.6 cc), the cardiac output per minute decreased, the cardiac index<sup>14</sup> decreased (range, 1.35 to 1.84 liters), the stroke volume decreased (range, 20 to 42 cc), the venous pressure elevated (range, 17.9 to 24 cm) and the circulation time prolonged (range, fifteen and four-tenths to twenty-nine and eight-tenths seconds) (table 1 and figs 1 to 5).

After operation all the measurements approached or attained normal levels, in short, the arteriovenous oxygen difference approached or became normal (range, 51.4 to 68.7 cc), the cardiac output per minute

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9 Tarr, L., Oppenheimer, B. S., and Sager, R. V. The Circulation Time in Various Clinical Conditions Determined by the Use of Sodium Dehydrocholate, *Am Heart J* 8:766, 1933. Stewart, H. J., Crane, N. F., and Detrick, J. E. Studies of the Circulation in Pernicious Anemia, *J Clin Investigation* 16:431, 1937.

10 Taylor, F. A., Thomas, A. B., and Schleiter, H. G. A Direct Method for the Estimation of Venous Pressure. *Proc Soc Exper Biol & Med* 27:867, 1930.

11 The members of the Roentgenographic Department of the New York Hospital cooperated in this investigation.

12 Levy, R. L. The Size of the Heart in Pneumonia. A Teleroentgenographic Study, with Observations on the Effect of Digitalis Therapy, *Arch Int Med* 32:359 (Sept.) 1923.

13 Bardeen, C. R. Determination of the Size of the Heart by Means of X-Rays, *Am J Anat* 23:423, 1918.

14 The cardiac index represents the cardiac output in liters per square meter of body surface per minute.

increased, the cardiac index increased (range, 1.8 to 2.72 liters), the stroke volume increased (range, 33 to 50 cc), the venous pressure fell (range, 8.3 to 16.7 cm) and the circulation time became shorter (range, seven and three-tenths to seventeen and one-tenth seconds) (table 1 and figs 1 to 5)

In certain cases the heart rate was elevated before operation and became slower afterward, and in others the reverse happened

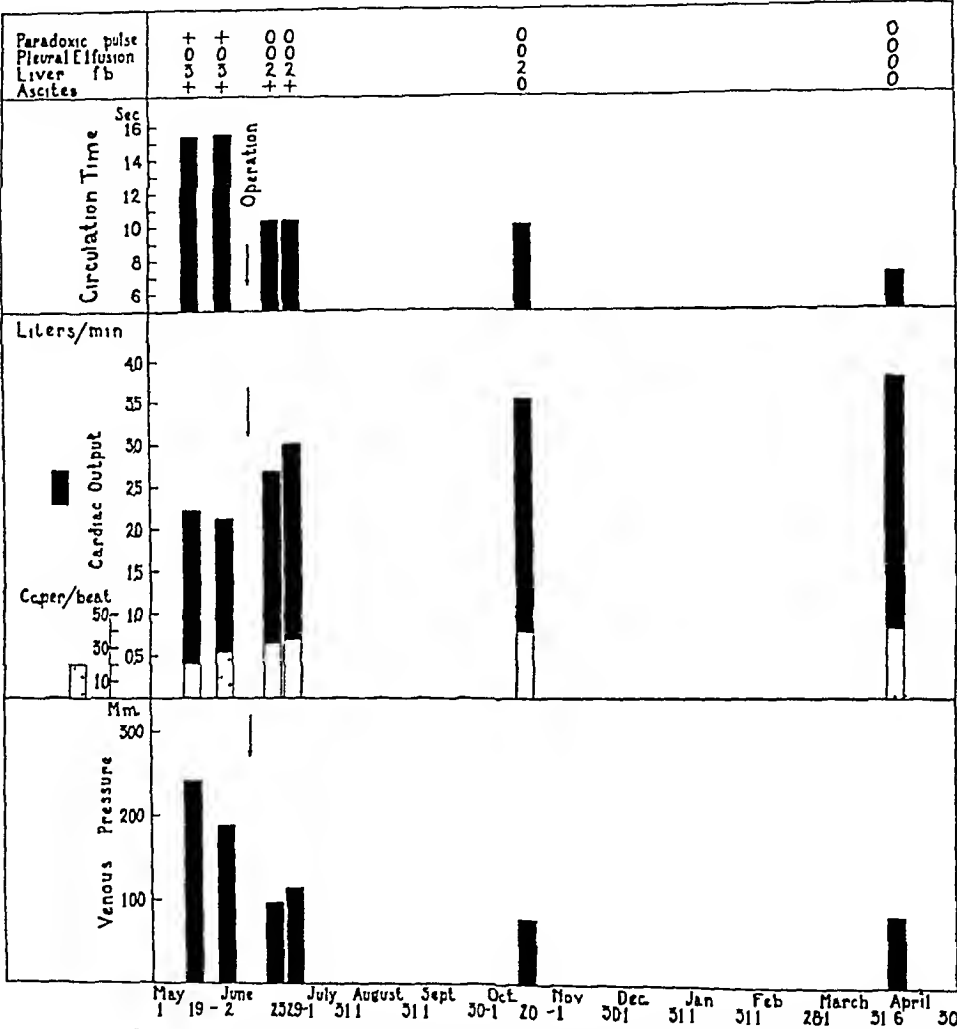


Fig 1—In this figure are plotted data relating to the cardiac output, venous pressure, circulation time and clinical signs in case 1, before and after pericardial resection. In this chart and some of the following charts *fb* indicates fingerbreadths and *Umb*, to the umbilicus

The basal metabolic rate was not altered significantly from normal in the presence of this syndrome, nor did pericardiectomy change it. The serum protein value was low in 2 cases (cases 5 and 6) and in the normal range in the others.

The vital capacity before operation was in the normal range unless there was pleural effusion. In certain cases it increased after operation,

in others the decrease was probably to be accounted for by the flexibility of the thoracic cage occasioned by removal of the ribs

Preoperative infra-red photographs revealed an increase in the number, caliber and distention of the superficial veins After operation the

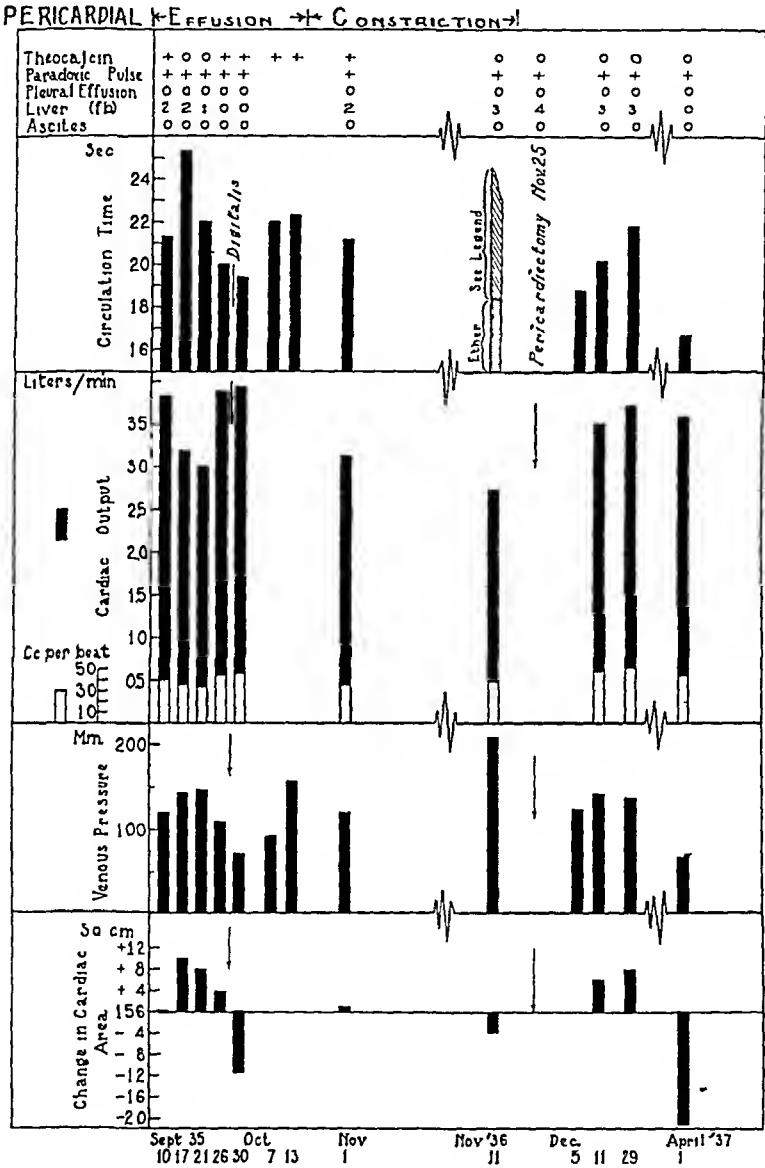


Fig 2—In this figure are plotted data relating to case 2 Because the patient was sensitive to decholin at this time it could not be used "Ether time" is shorter than "decholin time," since the former is the arm to lung time and the latter the arm to tongue time

veins became less conspicuous, and many channels became invisible (figs 6 to 9)

Distention of the veins of the eyegrounds was marked before operation and decreased with the fall in venous pressure after operation

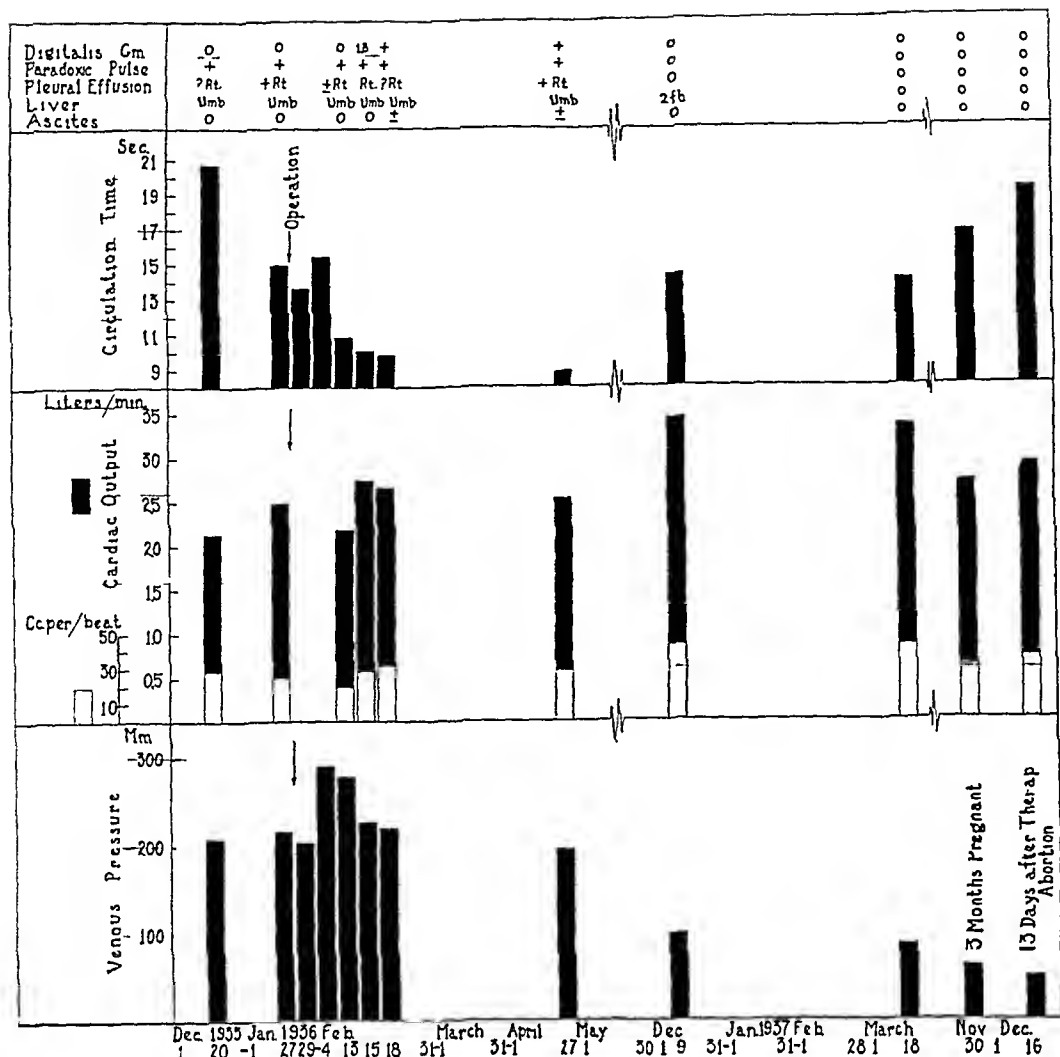


Fig 3—In this figure are plotted data relating to case 3

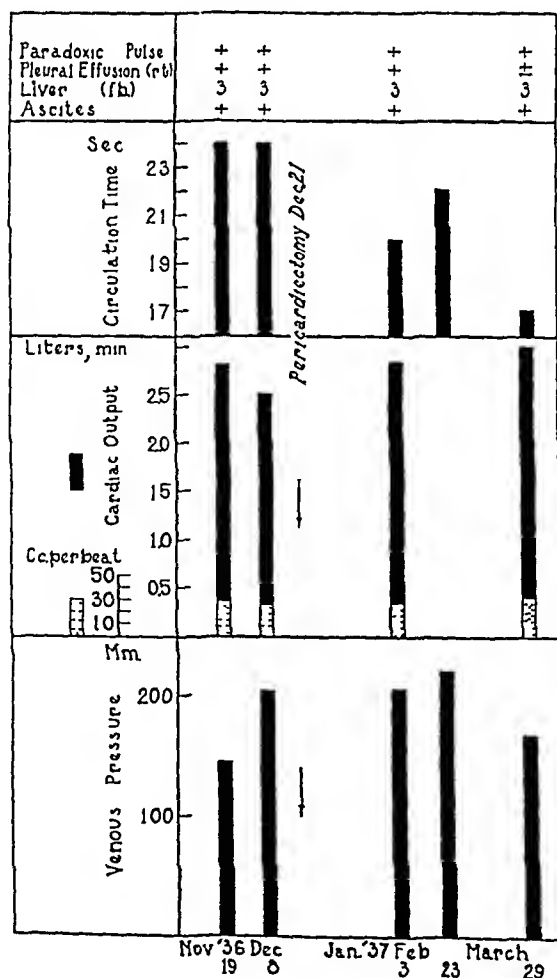


Fig 4—In this figure are plotted data relating to case 4

TABLE 1—Data Relating to Nine Patients Suffering from Chronic

Case, Age, Sex	Date	Weight, Kg	Arterio- venous Oxygen Differ- ence, Cc	Cardiac Output, L per Min	Cardiac Output, L per Sq M per Min	Stroke Volume, Cc	Arterial Pressure, Mm Hg	Cardiac Area, Sq Cm	Left Ventric- ular Work, Gm M per Beat	Circu- lation Time, Sec	Venous Pres- sure, Cm	Vital Capacity, Cc
1 15 yr F	5/19/36	40.9	71.7	2.23	1.70	20	93/84	82.2	24.2	15.4	24.0	1,900
	6/2/36	37.0	66.5	2.12	1.70	21	82/70	79.9	27.9	15.5	18.8	1,850
	6/5/36	(operation)										
	6/8/36										17.5	
	6/23/36	34.7	52.1	2.67	2.20	32	85/60	86.4	31.8	10.4	9.6	1,350
	6/29/36	34.7	48.5	3.00	2.42	34	86/55	90.7	37.3	10.4	11.4	1,500
	10/20/36	39.7	43.3	3.53	2.70	39	90/63	93.3	41.9	10.1	7.8	1,800
	4/6/37	44.9	51.1	3.78	2.72	41	100/60	113.5	44.6	7.3	8.8	1,600
2 36 yr M	9/10/35	56.7	51.9	3.83	2.23	40	104/70	156.0	47.3	21.3	12.0	3,200
	9/17/35	58.2	62.5	3.18	1.87	36	94/64	166.2	38.7	25.3	14.3	3,100
	9/21/35	58.7	66.6	3.00	1.72	34	94/60	164.2	35.6	22.0	14.8	2,900
	9/26/35	58.0	53.9	3.88	2.28	45	93/63	159.8	50.8	20.0	11.0	3,500
	9/29/35											
	9/30/35	57.2	54.5	3.93	2.38	47	102/64	144.4	53.1	19.4	7.8	3,800
	10/7/35									22.0	9.3	
	10/13/35									22.3	15.7	
	11/1/35	60.3	71.0	3.13	1.82	36	96/63	157.0	40.1	21.2	12.2	3,200
	11/11/36	59.5	74.2	2.74	1.60	39	115/90	152.1	54.6	18.4	21.0	1,800
	11/25/36	(operation)								(ether)		
	12/5/36									18.8	12.5	(Not basal)
	12/11/36	54.7	56.3	3.51	2.14	49	95/63	162.1	54.6	20.2	14.3	1,800
	12/29/36	57.2	53.4	3.73	2.25	52	105/78	164.1	65.1	21.8	13.8	2,500
	4/1/37	53.8	53.8	3.59	2.19	45	95/75	134.6	52.0	16.7	7.1	1,900
	1/28/38									19.2	9.2	
3 30 yr F	12/20/35	42.7	88.6	2.14	1.55	29	92/66		31.1	20.7	20.8	1,500
	1/27/36	45.9	81.2	2.48	1.76	25	92/70		27.5	15.0	21.5	1,500
	1/28/36	(operation)										
	1/29/36									13.7	20.3	
	2/4/36									15.5	29.0	
	2/13/36	47.7	85.0	2.19	1.52	20	110/82		24.0	10.9	27.8	1,000
	2/14/36											
	2/15/36	46.8	66.7	2.76	1.94	29	96/64		32.0	10.2	22.7	900
	2/18/36	47.5	73.5	2.65	1.84	32	105/75		39.0	9.9	22.0	950
	4/27/36	48.4	71.8	2.54	1.70	29	108/72		35.5	9.0	19.3	1,400
4 20 yr M	12/9/36	49.9	57.2	3.44	2.34	43	105/75	120.3	52.6	14.4	9.8	2,000
	3/18/37	51.5	54.9	3.35	2.25	42	80/50	119.0	37.0	14.0	8.5	2,600
	11/30/37	50.3	70.3	2.70	1.84	31	100/60	106.5	33.7	17.6	6.0	2,800
	12/16/37	49.7	62.4	2.90	2.00	36	90/65	104.4	33.2	12.4	4.8	2,850
	11/19/36	61.3	81.2	2.81	1.63	29	98/70	165.5	33.1	24.0	14.5	1,400
	12/8/36	61.5	81.7	2.51	1.44	26	100/70	155.6	30.0	24.0	20.4	1,400
	12/21/36	(operation)										
	2/3/37	61.4	76.6	2.84	1.57	28	105/80	172.5	35.8	20.0	20.5	1,300
	2/23/37									22.1	22.0	
	3/29/37	59.4	68.7	3.01	1.80	33	90/70	170.9	35.9	17.1	16.7	2,000
5 44 yr F	1/29/38	65.1					110/80	163.7		21.5	18.8	1,700
	8/21/36	64.0	83.1	2.22	1.35	34	127/116/78	141.1	45.8	18.6	17.9	1,650
	9/22/36	57.0	71.5	2.69	1.71	34	123/72	129.4	46.2	18.4	13.8	2,250
	9/28/36	(operation)										
	11/12/36									13.3	16.1	
6 38 yr F	12/10/36	43.9	61.8	2.78	2.01	43	110/70	135.5	52.6	11.2	11.3	1,200
	3/31/37	57.7	75.3	2.78	1.76	35	128/68		46.8	16.7	19.8	1,400
	2/1/38	58.1	64.2	3.16	2.02	38	100/80		56.5	19.2	15.3	750
	5/26/37	104.3	59.7	4.66	2.20	42	130/75	124.8	58.8	12.5	20.1	2,000
	6/15/37	93.2	58.3	4.31	2.16	49	118/70	130.3	62.6	13.5	12.7	2,800
	6/17/37	(operation)										
	7/1/37	88.0					110/88			10.2	11.1	1,800
	8/6/37									9.0	10.2	
	8/27/37	72.0	61.0	3.67	2.05	47	95/65	147.1	51.1	16.7	12.9	3,350
	11/19/37	72.4	65.5	3.39	1.88	46	120/80	142.4	62.6	18.0	10.7	3,450
7 58 yr M	11/26/37	73.8					85/63			19.5	8.7	3,600
	1/28/38	86.9	56.5	3.89	2.00	50	105/75	150.3	61.2	21.4	8.3	2,900
	1/19/38	80.9	72.8	3.16	1.62	61	135/95	183.9	95.4	29.8	22.3	3,300
	2/5/38	74.6	73.8	3.35	1.84	54	150/98	162.4	91.1	25.9	7.3	4,100
	4/12/38	84.6					160/145/100			35.5	25.9	
8 29 yr M	4/26/38	(operation)										
	6/13/38	74.0	76.8	3.00	1.59	48	142/90	194.8	75.7	28.9	16.4	2,800
9 13 yr M	6/1/35	70.6	81.9	2.99	1.60	34	104/94/68	165.1	33.4	22.8	18.2	4,600
	12/11/34	49.7	74.7	2.69	1.82	32	123/70	99.5	43.1	10.6	14.5	1,600

\* In all except cases 5 and 7 there was normal sinus rhythm. The serum protein values were repeatedly shown to lie within normal limits in all except cases 5 and 6, in which the total protein value repeatedly remained between 4 and 5 Gm. On the days when special studies of the circulation were made, maintenance doses of digitals or doses of other drugs were not given until after the studies had been completed.

† 0 indicates absent, +, present, ±, doubtful or questionable, ↑, increased, ↓, decreased.

# Constrictive Pericarditis, Seven of Whom Had Pericardiectomy

Drugs, Gm	Evidence of Congestive Heart Failure†							Para- doxic Pulse‡	Red Blood Cells, per Millions Cu Mm		Hemo- globin, %‡	Comment
	Dyspnea	Cyanosis	Rales	Enlargement of Liver	Ascites	Edema	Pleural Effusion					
Aminophylline, 0.3	0 0	0 0	0 0	+	+	0 0	0 0	+	3.8 4.3	76 80	Mercupurin (a mercurin theophylline preparation) (1 cc) was given intravenously on May 17, 1936	
0	0	0	0	+↑	+↑	0	0	0	4.8	80		
0	0	0	±	+	+	0	0	±	4.1	92		
0	0	0	0	0	0	0	0	±	4.9	100		
Theocalcin, 4.5	+	+	0	+	0	0	0	+	5.8	112	No theocalcin was given between September 10 and 17, no theocalcin was given between November 6 and 11	
0	0	+	0	0	0	0	0	+				
0	+	+	+	+	0	0	0	+				
0	0	0	0	0	0	0	0	+				
Theocalcin, 4.5	0	0	0	0	0	0	0	+				
Digitalis, 1.8	0	+	0	0	0	0	0	+				
Theocalcin, 4.5	0	+	0	0	0	0	0	+				
Theocalcin, 4	0	0	0	0	0	0	0	+				
Theocalcin, 4	0	0	0	+	0	0	0	+				
Theocalcin, 3	0	0	0	+	0	0	0	+	5.0	92		
0	+	+	0	+↓	0	0	0	+				
0	0	+	0	+↑	0	0	0	+				
0	0	+↑	0	+	0	0	0	+	5.1	102		
0	0	0	0	0	0	0	0	+	5.3	106		
0	0	0	0	0	0	0	0	0				
0	0	0	0	0	0	0	0	0				
Digitalis, 0.2, ammonium chloride, 3	0	+	+	+	0	0	Rt	+	4.3	80	No digitalis was given between Dec 28, 1935, and Jan 27, 1936, mercupurin (a mercurin theophylline preparation) (2 cc) was given intravenously on Jan 26, 1936, no digitalis was given between March 5 and April 27, 1936, on March 18, 1937, the patient was pregnant, therapeutic abortion, by means of miniature cesarean section, was performed on December 3	
Ammonium chloride, 3	0	+↓	+	+	0	0	Rt	+				
.	±	0	+↓	+	0	0	Rt	+	3.9	77		
0	0	+	+	+	0	0	Rt	+				
Digitalis, 1.8	0	0	+	+	0	0	Rt	+				
0	0	+	+	+	±	0	Rt	+				
Digitalis, 0.2	0	+	+	+	±	0	Rt	±	4.4	82		
0	0	0	+↑	+↑	0	0	0	0	4.3	84		
0	0	0	+↑	0	0	0	0	0	4.5	100	Mercupurin (a mercurin theophylline preparation) (2 cc) was given intravenously on Feb 1, 1937	
0	0	0	0	0	0	0	0	0	4.0	80		
0	0	0	0	0	0	0	0	0	4.1	87		
0	+	+	+	+	+	0	Rt	+	5.7	104		
0	0	+	+	+	+	0	Rt	+	5.2	100	Mercupurin (a mercurin theophylline preparation) (2 cc) was given intravenously on Sept 21, 1936, theocalcin (1.5 Gm three times daily) and ammonium chloride (1 Gm twice daily) were also being given	
Ammonium chloride, 3	0	+	+	+	+↑	0	Rt	+	5.0	100		
Ammonium chloride, 3	0	0	0	+	±	0↑	Rt	+	5.6	110		
Ammonium chloride, 3	0	±	+	+	+	+	Rt	+				
Urea, 30	0	±	+	+	+	+	Rt	+			Mercupurin (a mercurin theophylline preparation) (2 cc) was given intravenously on Sept 21, 1936, theocalcin (1.5 Gm three times daily) and ammonium chloride (1 Gm twice daily) were also being given	
Digitalis, 0.1	0	+	+	+	+	+	Rt	+	5.1	122		
Digitalis, 0.1	0	+	0	+	±	+	Rt	+	5.3	104		
Digitalis, 0.2, ammonium chloride, 3	0	+	0	+	0	+↑	Rt ↑	+	4.0	78		
Digitalis, 0.2, ammonium chloride, 3	+	+↓	+	+	+	+↓	Rt ↓	+	4.3	96	Mercupurin (a mercurin theophylline preparation) (2 cc) was given intravenously on Nov 17, 1937, theocalcin (1 Gm three times daily) and ammonium chloride (1 Gm three times daily) were also being given	
Digitalis, 0.2, aminophylline, 0.3	+	+	+	+	+?	+	Rt	+				
Digitalis, 0.2, urea, 45	+	+	+	+	+	+		+	5.5	110		
0	+	+	+	+	+	+	0	+	4.8	90		
Theocalcin, 4.5	0	0	+↓	+↓	+↓	+	0	+				
0	0	+	0	+	+	+↓	0	+	4.8	90		
Ammonium chloride, 3	0	0	0	+	±	+↓	0	+	4.9	86		
0	0	0	0	+↓	±	0	0	+	5.9	96		
Ammonium chloride, 3, theocalcin, 3	0	0	0	+	0	0	0	±			Mercupurin (a mercurin theophylline preparation) (2 cc) was given intravenously on Feb 4, 1937	
Ammonium chloride, 3	±	±	0	+	±	+	0	+				
Digitalis, 0.1, ammonium chloride, 6	0	+	0	+	0	±	0	+	5.4	114		
Digitalis, 0.1, ammonium chloride, 6	0	+↓	±	+↓	0	0	0	+				
Digitalis, 0.1, ammonium chloride, 6	+	+	±	+	0	0	0	+	4.7	94	This patient was referred for study by Dr Ralph Boots	
Digitalis, 0.1, ammonium chloride, 6	0	±	0	+	0	0	0	+				
0	0	+	0	±	0	0	0	+	5.4	118		
0	0	0	0	0	0	0	0	±	5.8	95		
0	0	0	0	0	0	0	0	±	5.8	95	Referred by Dr Richmond L. Moore§	

† In this report 14.5 Gm of hemoglobin was taken as equivalent to 100 per cent

§ "Resting" and not "basal" measurements

¶ This patient had suffered from purulent pericarditis for ten months before these observations were made, and this had been cured by surgical drainage (Moore, R. L. Ann Surg 102: 980, 1935)

There were limitation of motion of the cardiac chambers and fixation of the heart on fluoroscopic examination. In 4 cases (cases 1, 5, 7 and 8) calcification was observed. After operation the extent of contraction increased in all cases.

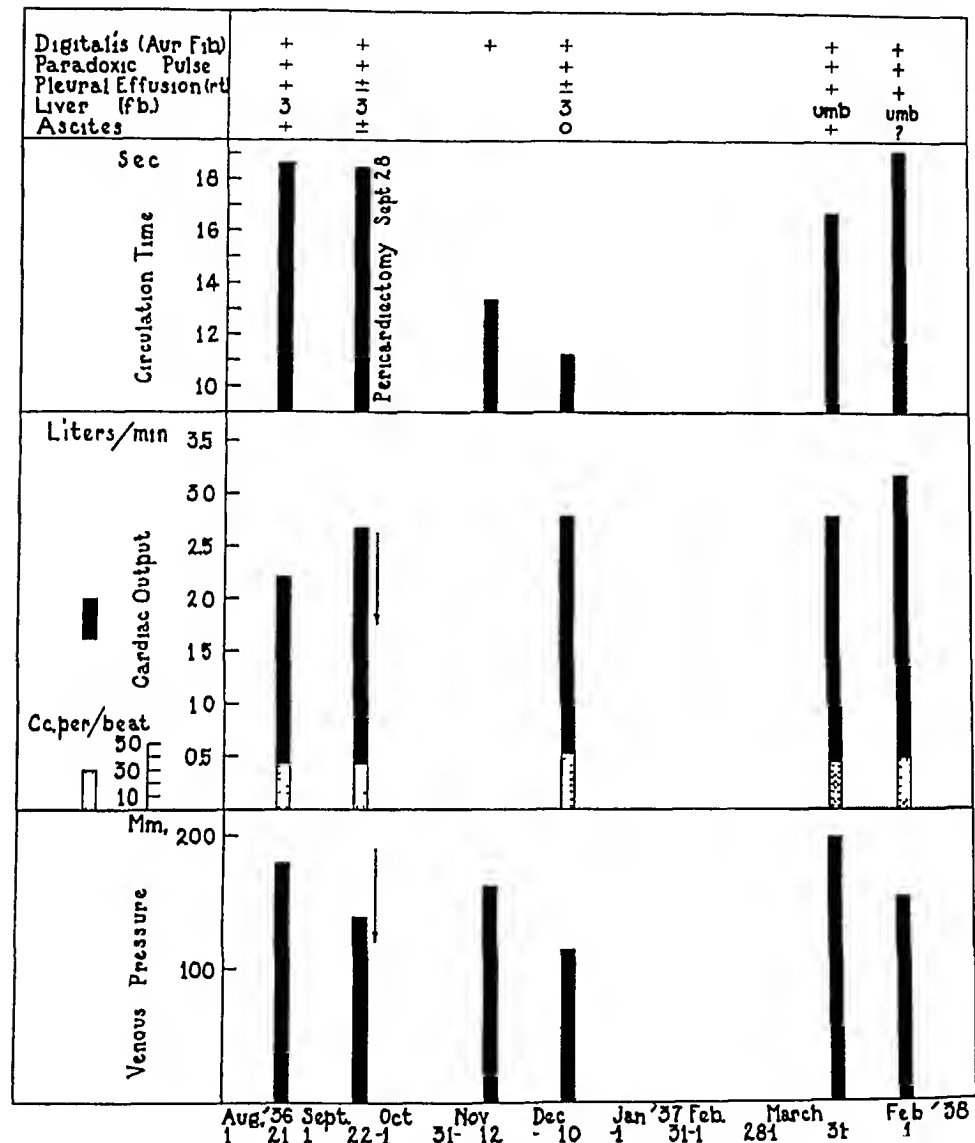


Fig 5—In this figure are plotted data relating to case 5

The size and shape of the cardiac silhouette<sup>15</sup> was not uniform. In 7 cases it was moderately large (cases 2 [fig 10], 3, 4, 5 [fig 11], 7, 8 [fig 12] and 9) and in 2 conspicuously small (cases 1 [fig 13]

15 It is recalled that the cardiac silhouette includes the shadow of the heart together with the thickened pericardium and that the cardiac size may be small though the shadow is large

and 6) Lateral views revealed calcification in 4 cases (cases 1 [fig 3], 5 [fig 11], 7 and 8 [fig 12]) In 2 of the cases (cases 1 [fig 3] and 6) in which operation was performed there was a decrease in the size of the heart, in 3 (cases 2 [fig 10], 3 and 7) there was an increase and in the other 2 (cases 4 and 5 [fig 11]), there was no change

#### MEDICAL TREATMENT

The medical treatment has been similar to that used in cases of heart failure, with the exception of the use of digitalis The patients were given a low salt diet (2 Gm daily), and the intake of fluid was limited to 1,200 cc Liberal amounts of protein were given because of the low value for serum protein in 2 cases and in order to maintain the level of the serum protein in the others

Digitalis was given to 2 patients (cases 5 and 7) exhibiting auricular fibrillation, to keep the cardiac rate slow We were unable to attribute any particular diuretic effect to its use in these cases

We found mercurpurin (a mercurin-theophylline preparation) the most satisfactory drug to use to mobilize fluids (Stewart and Wheeler<sup>16</sup>) It was usually given in 2 cc doses intravenously at three day intervals Ammonium chloride (3 Gm a day) was given to certain patients to enhance the diuretic effect Theocalcin (4.5 Gm daily) was given at other times Urea (50 per cent solution) was given twice a day in 30 cc doses to 1 patient Aminophylline (0.1 Gm three times a day) was used on other occasions Abdominal and thoracic paracenteses were used if other measures were not effective Pericardiectomy was carried out when the patient had attained a suitable state, afterward the drugs for mobilization of fluid were continued if necessary Giving mercurpurin in case 6 resulted in only slight diuresis before operation, after pericardiectomy, however, 5,000 cc of urine was secreted on the day of the injection Diuretics were given after operation as long as necessary They were not required in cases 1 and 2, while in case 3 mercurpurin (a mercurin-theophylline preparation) was required for twelve months after operation Two patients (cases 4 and 6) became ambulatory with weekly injections of mercurpurin In case 5 the use of urea maintained the output of urine to amounts that prevented too great an accumulation of fluid, and the patient was able to carry on her household activities

#### CLINICAL FEATURES

The histories of the 9 patients we have observed, together with the correlation of the manifestations on physical examination and the measurements of the circulation, are as follows

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16 Stewart, H J, and Wheeler, C H The Use of Mercurpurin in the Treatment of Congestive Heart Failure and in the Mobilization of Excess Body Fluid, *Am Heart J* **14** 526, 1937



TABLE 2—Summary of Clinical Manifestations in Nine Cases of Chronic Constrictive Pericarditis, Pericardial Resection Being Performed in Seven Cases<sup>a</sup>

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9
Age	15 years	36 years	30 years	20 years	44 years	38 years	58 years	29 years	13 years
Sex	Female	Male	Female	Male	Female	Female	Male	Male	Male
History of rheumatic infection	Present	Absent	Absent	Absent	Present	Absent	Absent	Absent	Absent
History of valvular heart disease	Absent	Absent	Absent	Absent	Absent	Absent	Absent	Absent	Absent
History of tuberculous infection	Present	Absent	Absent	Absent	Absent	Absent	Absent	Absent	Absent
History of nonspecific pulmonary infection just before onset of symptoms	Absent	Present	Absent	Absent	Absent	Present	Absent	Absent	Present
History of pericarditis or pericardial effusion	Absent	Present	Absent	Present	Absent	Absent	Absent	Absent	Present
Cause found at operation	Unknown	Unknown	Tuberculosis	Unknown	Unknown	Unknown	Swelling of ankles and dyspnea	Ache in epigastric region	None
Chief symptoms†	Swelling of abdomen, loss of weight and dyspnea	Dyspnea, edema, ache in epigastric region and "fullness" in head	Dyspnea, weakness and swelling of abdomen	Swelling of abdomen and dyspnea	Swelling of abdomen	Swelling of ankles and dyspnea	Swelling of ankles and dyspnea	Ache in epigastric region	None
Signs of heart failure before operation									
Dyspnea	Absent	Present	Present	Doubtful	Absent	Present	Absent	Absent	Absent
Cyanosis	Present	Present	Present	Doubtful	Present	Present	Doubtful	Present	Absent
Distention of neck veins	Present	Present	Present	Present	Present	Present	Present	Present	Absent
Rales	Absent	Absent	Present	Present	Doubtful	Doubtful	Doubtful	Absent	Absent
Fluid in chest	Absent	Present	Present	Present	Present	Present	Present	Present	Absent
Enlarged liver	Present	Absent	Present	Present	Present	Doubtful	Doubtful	Absent	Absent
Ascites	Present	Absent	Present	Absent	Present	Present	Doubtful	Absent	Absent
Edema	Absent	Absent	Present	NS R	Present	Present	Doubtful	Absent	Absent
Rhythm‡	NS R	NS R	NS R	NS R	A F	NS R	A F	NS R	NS R
Paradoxical pulse	Present	Present	Present	Present	Present	Present	Present	Present	Present
Blood pressure	Low	Low	Low	Low	Normal	Normal	Slightly high	Low	Normal

Low pulse pressure	Present	Present	Present	Present	Present	Absent	Absent	Present	Absent
Venous stasis in infra red photo graph	Present	Present	Present	Present	Present	Doubtful	Present	Present	Absent
Fluoroscopic examination of heart	Present	Present	Present	Present	Present	Present	Present	Present	Present
Decreased pulsations	Present	Present	Present	Present	Present	Moderate	Present	Present	Present
Shift of heart with change in patient's position	Very slight	Very slight	Very slight	Very slight	Very slight	None	None	None	None
Size of heart in roentgenogram	Very small	Large	Slightly enlarged	Large	Large	Large	Small	Slightly enlarged	Slightly enlarged
Calcification of pericardium	Present	Absent	Absent	Absent	Absent	Present	Absent	Present	Absent
In roentgenogram	Present	Absent	Absent	Absent	Absent	Present	Absent	Present	Absent
At operation	Present	Absent	Absent	Absent	Absent	Present	Absent	Present	Absent
On microscope examination§	Present	Present	Absent	Absent	Absent	Present	Present	Present	Present
Electrocardiogram	Present	Present	Absent	Absent	Absent	Present	Present	Present	Present
QRS, leads I to III	Low ampl	Low ampl	Low ampl	Low ampl	Low ampl	Low ampl	Low ampl	Low ampl	Low ampl
T wave	I to III, low ampl, II and negative III, cove shaped	I to III, low ampl	I to III, low ampl	I to II, cove shaped	I to III, diphase	I to III, low ampl	III, low ampl	II and III, negative, cove shaped	Normal ampl
AxIs deviation	Slight, right	Right	Slight, right	Slight, left	Slight, right	Slight, right	Slight, left	Slight, right	Slight, left
Shift of electrical axis	37 degrees	None	11 degrees	11 degrees	35 degrees	35 degrees	None	None	None
Venous pressure	Increased	Slightly increased	Increased	Increased	Increased	Increased	Increased	Increased	Increased
Circulation time	Increased	Increased	Increased	Increased	Increased	Increased	Increased	Increased	Increased
Cardiac Index	Decreased	Decreased	Decreased	Decreased	Decreased	Decreased	Decreased	Decreased	Decreased
Cardiac output per beat	Decreased	Decreased	Decreased	Decreased	Decreased	Decreased	Decreased	Decreased	Decreased
Plasma protein value	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal
Duration of symptoms before operation	5 yr 6 mo	2 yr 8 mo	4 mo	1 yr 3 mo	2 mo	2 mo	6 yr	9 yr	10 mo
Result of medical treatment	Poor	Good	Poor	Poor	Fair	Fair	Poor	Fair	Fair
Result of operation	Cured	Cured	Cured	Improved	Improved	Improved	Improved	Convalescent from operation	Convalescent from operation
Time since operation	1 yr 9 mo	1 yr 4 mo	2 yr 2 mo	1 yr 3 mo	1 yr 6 mo	1 yr 6 mo	8 mo	1 mo	1 mo

\* Throughout this table leaders in a column indicate that the data were not available For further details the case histories should be consulted  
† The symptoms are listed in the order of severity  
‡ N S R indicates normal sinus rhythm, and A F, auricular fibrillation  
§ This refers to the examination of the pericardium elevated at operation  
|| Ampl indicates amplitude

CASE 1—A B, a girl aged 15 years, was admitted to the hospital on May 14, 1936. She suffered from acute polyarthritis when 6 years old. Four years later, swelling of the abdomen appeared. At exploratory laparotomy the diagnosis was tuberculosis of the peritoneum. Although swelling of the abdomen persisted, the patient felt well until four years later. Four months before admission to the hospital she suffered from a progressive increase in the size of the abdomen, dyspnea on exertion, weakness, anorexia and emaciation. On entry, emaciation, evidence of retarded development, moderate cyanosis, distention of the veins of the neck together with prominence of the superficial veins over the surface of the entire body, marked enlargement of the liver, signs of a large amount of ascitic fluid and a radial pulse of paradoxical type were observed. The heart sounds were faint. The blood pressure was 88 systolic and 52 diastolic. Other data are shown in table 2. With medical therapy, no appreciable change occurred.

The pericardium was resected on June 5. The heart was constricted within a greatly thickened, calcified pericardium whose two layers were adherent. Microscopic examination did not disclose the cause. Improvement was rapid without medication. On June 23 the radial pulse was no longer paradoxical, and all the signs of heart failure were much less marked. The patient was discharged and sent to the clinic on July 3. On August 3 the signs of ascites had disappeared. Enlargement of the liver was the only sign of congestion on October 20, but the organ was no longer palpable on December 4. One year and nine months after operation there was marked improvement in nutrition, with progress in development. She had been indulging in unrestricted physical activity, without symptoms and without recurrence of heart failure.

CASE 2—W M, a man aged 36 years, was admitted on July 26, 1935. Sixteen months earlier he suffered from an acute pulmonary infection associated with acute pericarditis. At the end of three months he experienced increasing dyspnea on exertion, orthopnea, a constant ache in the epigastric region, swelling of the ankles and weakness and at the end of twelve months was confined to bed. On admission to the hospital he showed marked dyspnea, cyanosis, orthopnea, distention of the veins of the neck, rales at the bases of both lungs, marked enlargement of the liver, signs of a small amount of ascitic fluid, marked pitting edema of the lower part of the legs and a paradoxical radial pulse. The rhythm of the heart was regular. The blood pressure measured 122 systolic and 90 diastolic. Other data are shown in table 2. With medical therapy marked improvement occurred, and three months later enlargement of the liver was the only sign of heart failure. The diagnosis was pericardial effusion with resorption. At the time of his discharge, on November 9, it was thought that he suffered from chronic constrictive pericarditis. A year later the symptoms and signs of heart failure recurred, and he returned to the hospital (Nov 9, 1936).

After medical preparation the pericardium was resected (November 25). The two layers of the pericardium were adherent and thickened and constricted the heart. Microscopic examination did not reveal the cause. Calcification was noted only on microscopic examination. The day after operation the distention of the veins of the neck was less. Four weeks later diuresis occurred spontaneously without drugs. On December 30 moderate cyanosis, distention of the veins in the right side of the neck and moderate enlargement of the liver were the only signs of heart failure, the radial pulse was only slightly paradoxical. The patient was discharged on December 30. One month later he indulged in ordinary physical

exertion, without distress. On March 15, 1937, slight enlargement of the liver was the only sign of heart failure. One and one-third years after operation the patient was actively at work and free from symptoms and signs of heart failure.

CASE 3—A R, a woman aged 29 years, was admitted on Dec 3, 1935. Twelve months before entry, during pregnancy, she experienced rapidly progressive weakness. In the fifth month of pregnancy she suffered from fever of unknown origin. Signs of heart failure and a paradoxical radial pulse developed during the sixth month of pregnancy. After delivery of a living infant in the eighth month of pregnancy, she continued to suffer from dyspnea on exertion, swelling of the ankles and weakness, with the addition of orthopnea and a progressive increase in the size of the abdomen. When admitted to the medical service four months later she showed dyspnea, cyanosis, orthopnea, marked distention

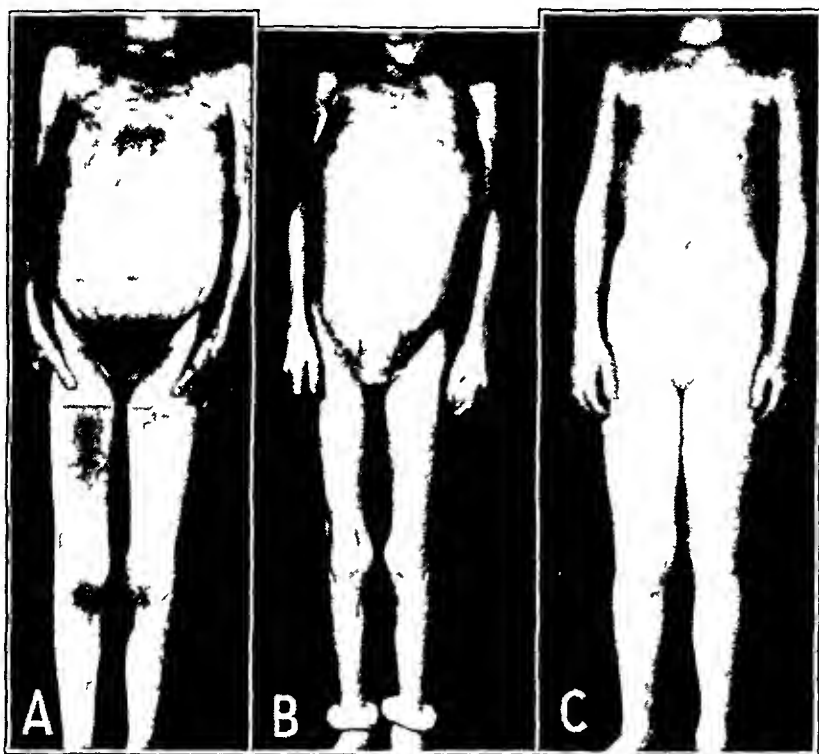


Fig 6—Infra-red photographs of A B (case 1) showing the change in the venous bed after pericardial resection. *A* was taken on May 20, 1936, before operation (performed on June 8), *B*, on June 29, about three weeks after operation, and *C*, on April 6, 1937, about ten months after operation, when the patient was "cured."

of the veins of the neck, signs of a large amount of fluid in the right pleural cavity, many moist rales at the base of the left lung, marked enlargement of the liver, signs of a large amount of ascitic fluid and moderate edema of the lower part of the legs. The radial pulse was paradoxical. The blood pressure measured 112 systolic and 76 diastolic. The heart sounds were faint. The rhythm of the heart was regular. Other data are shown in table 2. By medical means and seven thoracenteses (right), the dyspnea, orthopnea, signs of ascites and edema of the legs disappeared, and the signs of fluid in the right pleural cavity, the number of rales at the base of the left lung and the size of the liver all decreased.

On Jan 28, 1936, the pericardium was resected. The heart was constricted within a thickened pericardium, and the two layers, which were firmly adherent, showed active tuberculous infection without calcification. After operation, mercupurin (a mercurin-theophylline preparation) induced greater diuresis than before. The distention of the veins of the neck decreased, but the other signs of heart failure did not change significantly. The radial pulse remained paradoxical. The patient was discharged on March 5. She returned to the clinic weekly for injections of mercupurin. The symptoms and signs of heart failure gradually disappeared. By July 6 the patient was free from cardiac symptoms, although indulging in moderate physical exertion. By August 28 the radial pulse had lost its paradoxical

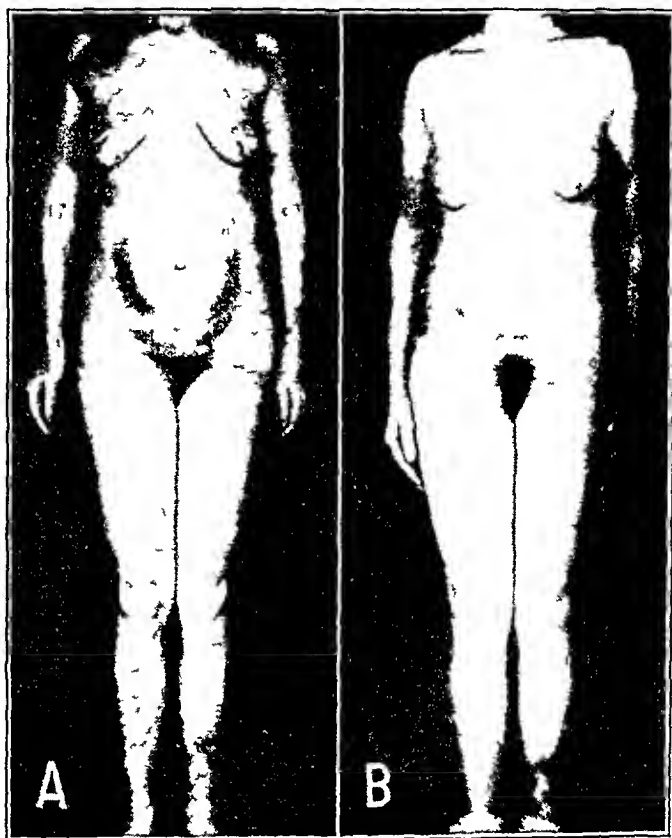


Fig 7—Infra-red photographs of A. R. (case 3). None were taken before operation. *A* was taken on Dec 9, 1936, about ten months after operation (performed on January 28), and *B*, nearly one year later, on Nov 30, 1937. In this case the improvement was slow, but the patient is now "cured."

characteristics. On December 9 a few rales at the base of the left lung, slight distention of the veins in the right side of the neck and moderate enlargement of the liver were the only signs of heart failure. On December 28 the use of drugs, including mercupurin was discontinued. By March 18, 1937, all the signs of heart failure had disappeared. The patient was engaging in unrestricted physical exertion, without symptoms. Two years and two months after operation the patient was still in excellent health.

CASE 4—J McC, a man aged 20 years, was admitted on Nov 18, 1936. Fourteen months earlier he suffered from pericardial effusion. Three months later he recovered and felt well until nine months before entry, when he experienced dyspnea on exertion, orthopnea, swelling of the ankles and recurrence of fever. The radial pulse was paradoxical. He again exhibited a large amount of pericardial effusion. After resting two months he attempted activity. The symptoms recurred, and, in addition, swelling of the abdomen appeared. Four months later he was admitted to the hospital, exhibiting slight dyspnea, slight cyanosis, moderate distention of the veins of the neck, rales at the base of the left lung, signs of a

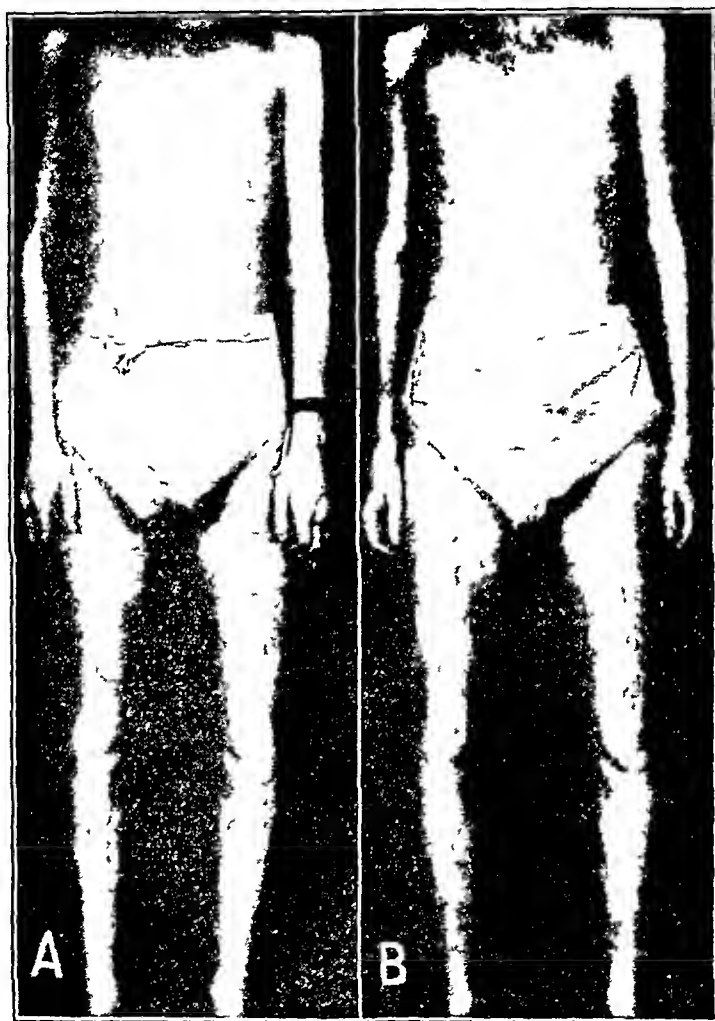


Fig 8—Infra-red photographs of J McC (case 4). *A* was taken on Nov 19, 1936, before operation (performed on December 21), and *B*, on March 29, 1937, more than three months after operation, when the patient was improved.

moderate amount of fluid in the right pleural cavity, marked enlargement of the liver, signs of a moderate amount of ascitic fluid and a paradoxical pulse. The blood pressure measured 98 systolic and 70 diastolic. Other data are shown in table 2. With medical therapy, slight improvement occurred.

On December 21 the pericardium was resected. The heart was constricted within a tough, fibrous pericardium, the two layers of which were closely fused. Microscopic examination revealed neither calcification nor the etiology. After opera-

tion mercupurin (a mercurin-theophylline preparation) induced more marked diuresis. A significant change in the signs of heart failure was not apparent on discharge, on March 3, 1937. The patient returned weekly for injections. By March 28 he was indulging in ordinary physical exertion, without symptoms. Slight distention of the veins of the neck, signs of a small amount of pleural effusion on the right side and of a small amount of ascitic fluid, moderate enlargement of the liver and a radial pulse of paradoxical type were present. One year and three months after operation the patient was indulging in ordinary physical exertion, commuting to college daily and leading a normal existence. The symptoms had not recurred, and the signs of heart failure appeared to be diminishing. He had been much improved by the operation but a "cure" had not been obtained.

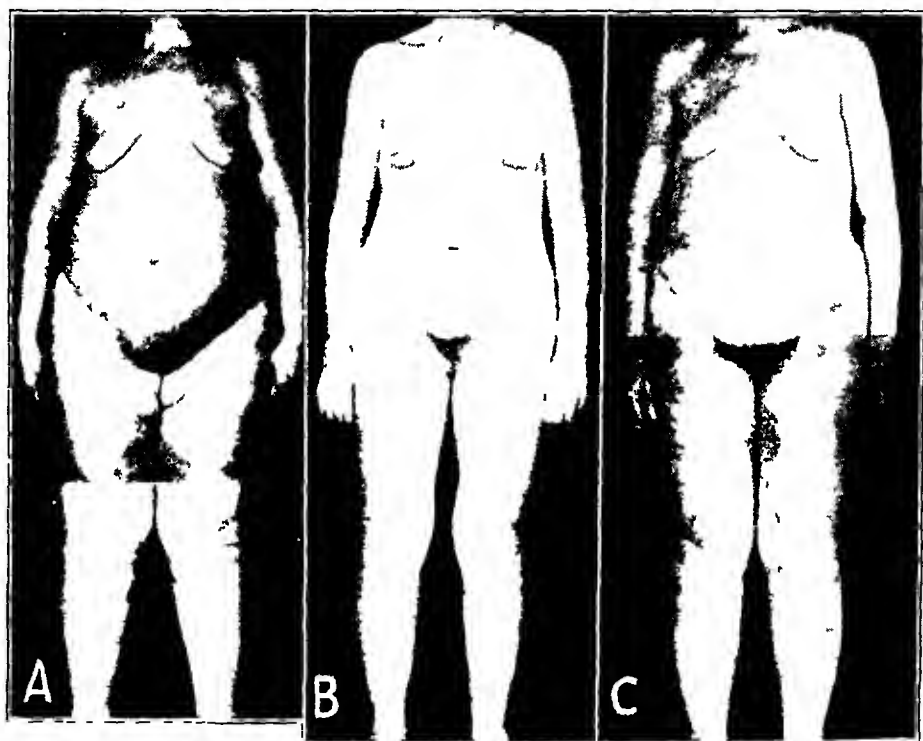


Fig 9—Infra-red photographs of J S (case 6). *A* was taken on May 26, 1937, when the patient was in her best state before operation (performed on June 17), *B*, on November 19, when she was free from signs of failure after operation, and *C*, on Jan 28, 1938, when she was ambulatory.

CASE 5—P A, a woman aged 44 years, was admitted on Aug 12, 1936. She had suffered from "pneumonia" and from an attack of acute polyarthritis at 20 and 30 years of age, respectively. Ten years before entry she observed swelling of the ankles occasionally. Two months before entry she experienced slight dyspnea on exertion, progressive increase in the size of the abdomen and persistent swelling of the ankles. She was given digitalis, without apparent benefit. Slight cyanosis, distention of the veins of the neck, signs of a moderate amount of fluid in the right pleural cavity, marked enlargement of the liver, signs of a large amount of ascitic fluid, massive pitting edema of the lower part of the legs and thighs, and a radial pulse of paradoxical type were present on entry. Auricular

fibrillation was noted. The blood pressure measured 110 systolic and 70 diastolic. Additional data are shown in table 2. With medical therapy the ascites disappeared, and the edema of the legs decreased markedly.

On September 28 the pericardium was resected. The heart was constricted within a markedly calcified pericardium whose two layers were closely fused and were adherent to the surface of the myocardium. The etiology was not discovered. After operation ammonium chloride and maintenance doses of digitalis were given daily, and mercupurin was used. On December 19 slight distention of the veins of the neck, signs of a small amount of fluid at the base of the right lung, marked enlargement of the liver, signs of a small amount of ascitic fluid and slight edema of the ankles were still observed. The radial pulse was still of paradoxical type. The patient was discharged on December 19. She received mercupurin during the first year, but its use was discontinued because of nausea and vomiting. After that she was given urea (30 Gm daily). For one and

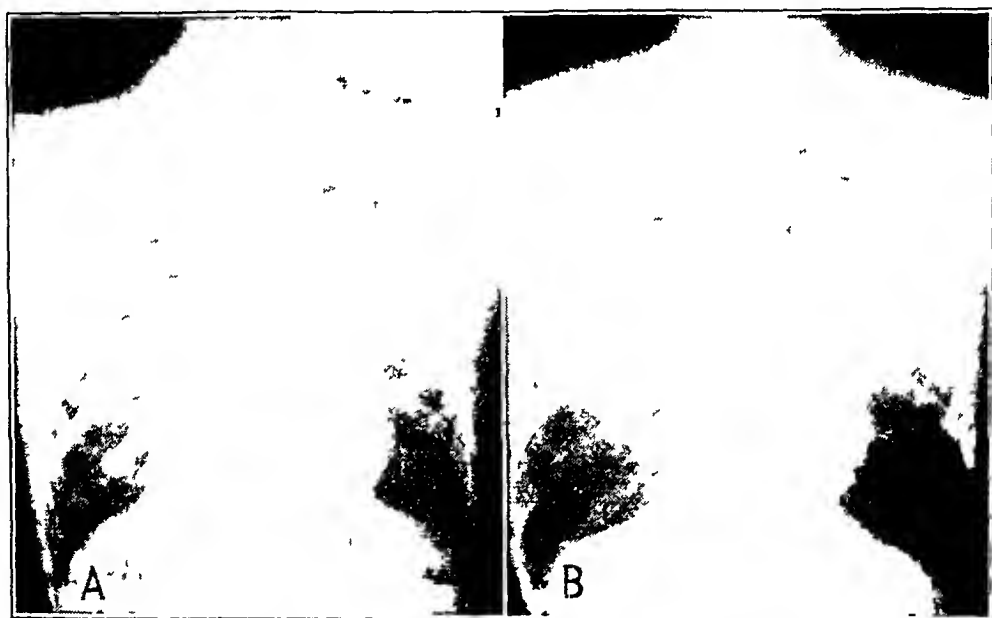


Fig 10—Roentgenograms of W M (case 2) taken at a distance of 2 meters. *A* was taken on Nov 11, 1936, before operation (performed on November 25), and *B*, on April 1, 1937, after operation. The size of the cardiac silhouette is seen to have decreased.

one-half years after operation the improvement was slow but definite. The patient could do housework without symptoms, and the signs of heart failure were not increased.

CASE 6—J S, a woman aged 38 years, was admitted on May 24, 1937. Six years earlier she suffered from an illness characterized by fever, cough and pain in the left scapular region on inspiration. These symptoms confined her to bed for three months. When she attempted activity she suffered from dyspnea on exertion, orthopnea and swelling of the ankles and abdomen. She was given digitalis and diuretics. Five and one-half years before entry thyroidectomy was performed. Her symptoms, however, became slowly more severe. On entry moderate dyspnea, orthopnea and cyanosis, distention of the veins of the neck, a few moist rales at the bases of both lungs, marked enlargement of the liver, signs



of a small amount of ascitic fluid, massive brawny edema of the lower part of the legs and thighs, and a radial pulse of markedly paradoxical quality were present. The blood pressure measured 130 systolic and 78 diastolic. The rhythm of the heart was regular. Other data are shown in table 2. With a medical regimen dyspnea and cyanosis disappeared, and the number of rales at the bases of the lungs, the size of the liver, the signs of ascites and the edema of the legs decreased.

On June 17 the pericardium was resected. The parietal pericardium was leathery, inelastic and loosely adherent to the visceral layer. Calcification was noted only on microscopic examination. The cause was not discovered. During the postoperative period, mercupurin (a mercurin-theophylline preparation) induced much more marked diuresis than formerly. On August 28 moderate enlargement of the liver and slight edema of the ankles only were present. The patient was discharged. She engaged in moderate physical exertion, and although mercupurin (a mercurin-theophylline preparation) was given weekly, signs of congestion increased slightly. Eight months after operation slight dyspnea, slight cyanosis, moderate distention of the veins of the neck, marked enlargement of the liver,

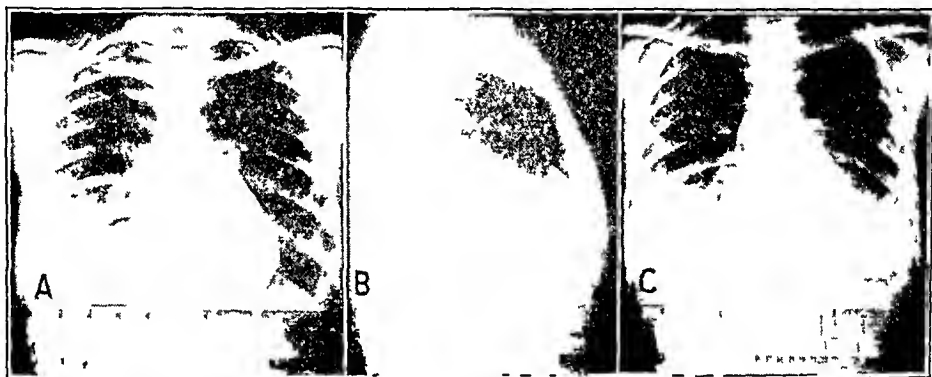


Fig 11—Roentgenograms of P A (case 5) *A* and *B* were taken on Sept 22, 1936, before operation (performed on September 28), and *C* was taken on December 10, after operation. Calcification can be seen in *A* as well as in *B*, a lateral view.

signs of a small amount of ascitic fluid, marked edema of the legs and the paradoxical radial pulse were still present. The patient's condition was, however, much improved (see the discussion of this case under the heading "Comment") over her pre-operative condition, and she was ambulatory.

**CASE 7**—R S, a man aged 58 years, was admitted on Jan 17, 1938. He was accepted for life insurance in 1929. Six years before admission to the hospital he experienced dyspnea on exertion and swelling of the ankles. The diagnosis was "hypertensive heart disease with heart failure." A roentgenogram of the heart at this time showed "marked dilatation of the left ventricle." He was given digitalis daily and stopped working, but in the six years preceding admission to the hospital the severity of his symptoms increased slowly and his activity became greatly limited. At entry, slight cyanosis, moderate distention of the veins of the neck, a few moist rales at the bases of both lungs, marked enlargement of the liver, signs of a small amount of ascitic fluid, slight edema of the ankles and the paradoxical radial pulse were present. The heart was enlarged to the left. The

rhythm was totally irregular. The blood pressure measured 155 systolic and 100 diastolic. Other data are shown in table 2. With a medical regimen the signs of heart failure diminished. Pericardiectomy was discussed with the patient. He was discharged on February 27, for consideration of operation. Although he indulged in slight physical exertion and mercupurin (a mercurin-theophylline preparation) was given weekly, dyspnea and swelling of the ankles recurred. The patient requested that pericardial resection be done and was readmitted on April 11. The signs of heart failure were essentially the same as at the time of the first entry. With medical treatment improvement occurred.

On April 26 the pericardium was resected. The two layers of the pericardium were everywhere adherent and the base and the right side of the heart were encased in a rigid, calcified shell. The cause was not disclosed on microscopic examination. His convalescence was slightly retarded by extravasation of sero-



Fig 12—A roentgenogram of C G (case 8), taken from an oblique angle (June 1, 1935). A wide rim of calcification is shown surrounding the heart.

sanguineous fluid between the heart and the soft tissue flap, which finally discharged at the lower angle of the incision. It is not yet possible to estimate the result of pericardiectomy.

CASE 8—C G, a man aged 29 years was admitted on June 5, 1935. Enlargement of the liver had been discovered nine years before. He exhibited no cardiac symptoms at this time and was not told that he had "heart trouble." Six years before entry he had "double pneumonia," and in the two years preceding entry he had three other attacks of "pneumonia," at intervals of about eight months. For four years he experienced aching and a sense of pressure in the epigastric region, which were exaggerated by exertion. These symptoms became more severe, and slight dyspnea on exertion and blueness of the lips appeared. When

admitted he showed marked cyanosis, distention of the veins of the neck, marked enlargement of the liver and a radial pulse of paradoxic type. The blood pressure measured 90 systolic and 70 diastolic. Other data are shown in table 2.

**CASE 9**—I F, a boy aged 13 years, was admitted on Dec 10, 1934. He had enjoyed excellent health until ten months prior to entry when he had "pneumonia" followed by "empyema of the pericardium." Four months later the pericardium was opened to secure drainage. After this the patient improved rapidly, gained 40 pounds (18 Kg) in weight and was cured. He was referred to the hospital for our studies. There were no signs of heart failure, but the radial pulse was paradoxic. The heart exhibited no abnormal signs. The blood pressure measured 116 systolic and 66 diastolic. Other data are shown in table 2.

*Comment*—From the summary (table 2) of the data for the 9 patients whom we have studied, it appears that the following manifestations contribute to the recognition of this syndrome. Signs of congestive heart failure are present in the absence of the usual, more

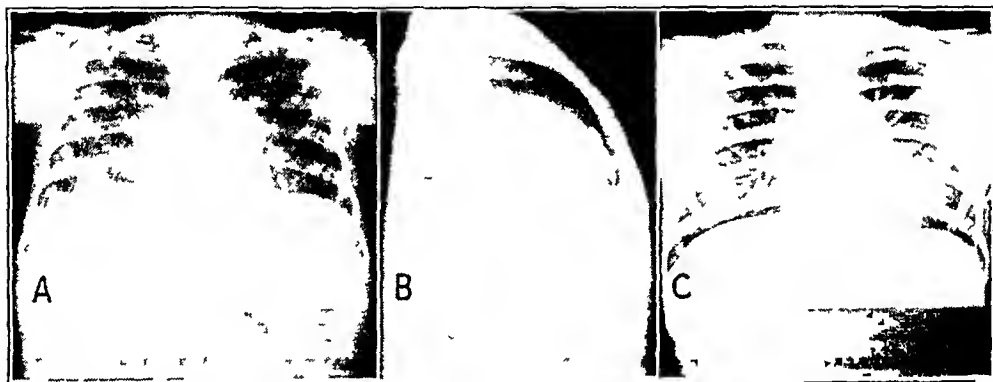


Fig 13—A, roentgenograms of A B (case 1). A and B were taken on June 2, 1936, before operation (performed on June 5), and C was taken on April 6, 1937, after operation. Calcification is shown in the lateral view (B), before operation.

common causes. Organic valvular lesions are conspicuously absent. Enlargement of the liver and ascites are usually present. Edema and pleural effusion occur, but less frequently. Distention of peripheral veins is a constant finding. The cardiac silhouette may be small, moderately enlarged or approximately normal. The point of maximal impulse may not shift. A paradoxic pulse was present in every case. The blood pressure is usually low and the pulse pressure small. Decrease or absence of motion of the several chambers of the heart may be observed. Calcification may be seen in the fluoroscope and in roentgenograms, though oblique views may be necessary to demonstrate it. It may be recalled, however, that calcification may be present without giving rise to obstruction. The electrocardiographic characteristics appear to be low amplitude of the QRS and T waves (fig 14). The T wave in leads I and II may be "cove" shaped. The electrical axis may not shift or may shift

only slightly (fig 14), too much emphasis is not to be placed on this finding, however. Slight right or slight left axis deviation may be present. A normal rhythm is usually present, though auricular fibrillation occurs in a few cases. Taking into consideration the operative procedures and the changes in the clinical state of the patient, it may be said that marked changes do not occur in the electrocardiogram after operation. Since 3 of our patients were observed during the stage of pericardial effusion, through the stage of absorption and then through the stage of constriction, this sequence is not uncommon. Patients suffering from pericardial effusion, in the absence of rheumatic valvular disease, should be observed continuously to be prepared for this development. We have been impressed with the absence of the usual rheumatic manifestations in these cases in which constriction has occurred, a point to which White<sup>1</sup> has already directed attention.

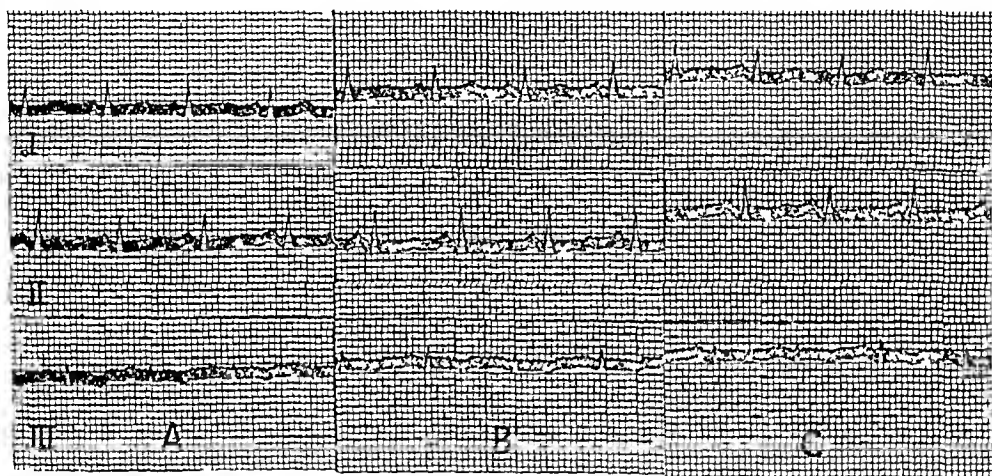


Fig 14—Electrocardiograms of J. S. (case 6) taken on May 26, 1937, before operation (performed on June 17). *A* was taken when the patient was lying on her back, *B*, when she was lying on her right side, and *C*, when she was lying on her left side. It is seen that the electrical axis remained practically fixed.

#### OPERATIVE TECHNIC

In the 7 cases in which operation was performed, ether anesthesia was used. The third, fourth, fifth and if necessary the second or sixth costal cartilages and the adjacent part of the ribs were resected on the left side.<sup>17</sup> The pericardium was incised over the left ventricle, mobilized and excised, after which a similar procedure was carried out over the right ventricle. The left ventricle was decompressed first, so it was ready to receive the increased amount of blood that was anticipated from decortication of the right ventricle. The pericardium was resected from as much of the anterior surface of the heart as possible without too great danger to the patient. The cardiac muscle herniated through the

defect in the pericardium in all cases. The skin-muscle flap was closed in layers. Since the periosteum of the ribs was left in place, regeneration and reformation of the bony part of the thorax occurred. Convalescence was rapid. The postoperative care was a continuation of the medical therapy, in 2 cases only was an oxygen tent used for a few hours after operation.

In 3 of the 7 cases in which operation was performed, "cure" has been obtained, and in 3 cases the condition has been improved. It is too early to foresee the result in the seventh case. These operative results, so far as they go, are an improvement over those previously reported. From the standpoint of the "cures" obtained, they are almost identical with those reported by Schmeiden, Churchill and Beck in cases in which the patients survived operation.<sup>17</sup>

#### COMMENT

Our studies show that the syndrome of chronic constrictive pericarditis is associated with decrease in the cardiac output per beat and per minute, rise in the venous pressure and slowing of the velocity of blood flow. The alteration in the circulation appears to be dependent on two defects. In the first place, the filling of the heart is compromised. This is apparent clinically on fluoroscopic examination in the finding of decreased filling of the heart in diastole, as well as when the heart is exposed at operation. In the second place, contraction is impaired, since on fluoroscopic examination and at operation decreased contractions of the heart are observed. These two defects result in a decrease in the cardiac output per minute and per beat and a piling up of blood on the venous side, which is observed objectively in the rise in venous pressure. The clinical manifestations of the disease appear to be associated with these alterations of the circulation. When clinical improvement or cure followed release of the heart by pericardial resection, parallel alterations of the circulation occurred toward or to normal levels, owing to greater filling of the heart in diastole and an increased discharge of blood in systole. These studies show parallelism between the physical signs and the objective circulatory impairment in these cases. They do not, however, elucidate the mechanism of certain signs which occur. That distention of veins and enlargement of the liver occur is to be expected. On the other hand, there has been no explanation of the occurrence of edema or of pleural effusion in certain cases and not in others. Venesection appears to be contraindicated in the presence of this syndrome, since the elevated venous pressure may represent the head of pressure which is required to maintain the circulation.

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<sup>17</sup> Heuer, G. J., and Stewart, H. J. The Surgical Treatment of Chronic Constrictive Pericarditis, to be published.

In case 6 the pattern of the measurements of the circulation did not conform with the pattern exhibited in the others, in this case the cardiac output per minute and the cardiac index were normal before operation (table 1). Improvement after operation, though marked, has now become stationary, measurements of the circulation did not alter significantly. There are several factors which may contribute to the deviation of the pattern exhibited by this patient from that of the others. In the first place, she had been subjected to partial thyroidectomy six years earlier, when it was thought that the signs of cardiac failure were due to hyperthyroidism. In the second place, the level of the serum protein has remained low. The patient may, in addition, exhibit vitamin deficiency, it did not seem justifiable, however, in the evaluation of pericardial resection to test this hypothesis until there was stabilization after pericardiectomy. The effect of thiamin chloride is now being observed. It is likely that the obstruction was removed at operation, because the venous pressure has fallen to normal limits and the size of the cardiac shadow has increased.

Three of these patients first came under observation when pericardial effusion was present (cases 2 [fig 2], 3 [fig 3] and 4 [fig 4]). Physical signs of obstruction (cases 3 and 4) and a change in the circulation characteristic of effusion (case 2) occurred. With absorption of fluid, the measurements of the circulation returned toward normal (case 2). Finally, when constriction began, signs of obstruction recurred, and impairment of the circulatory measurements appeared (case 2). The evolution of this process may require few (case 4) or many (cases 2 and 3) months.

Digitalis was given to 2 patients exhibiting auricular fibrillation to decrease the ventricular rate. The effect in 1 case (case 3 [table 1 and fig 3]) after operation was similar to that observed in the presence of heart failure,<sup>18</sup> namely, an increase in cardiac output, a fall in venous pressure and shortening of the circulation time. Fluid in the right pleural cavity prevented measurement of the cardiac size. The effect of digitalis on the circulation in another case (case 2 [table 1 and fig 2]) when pericardial effusion was present could not be evaluated with certainty because the studies intended for control were made four days before the drug was given, changes in the circulation not related to digitalis may have occurred during this time. The

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18 (a) Stewart, H. J., and Cohn, A. E. Studies on the Effect of the Action of Digitalis on the Output of Blood from the Heart. III. The Effect on the Output in Normal Human Hearts, the Effect on the Output of Hearts in Heart Failure with Congestion, in Human Beings, *J. Clin. Investigation* **11**:917, 1932. (b) Stewart, H. J., Detrick, J. E., Crane, N. F., and Wheeler, C. H. Action of Digitalis in Uncompensated Heart Disease, *Arch. Int. Med.* **62**:569 (Oct.) 1938.

use of this drug appears to be contraindicated except when auricular fibrillation is present. In other investigations we have found that digitalis decreases the size of the heart<sup>19</sup> and increases the extent of ventricular contraction<sup>20</sup>. In the case of the compressed, constricted heart, to decrease its size may amount to increasing the obstruction, on the other hand, it is likely that systolic contraction is as complete as is possible with the thickened, perhaps calcified, pericardium adherent to the organ. Whether other effects of the drug might counterbalance these two contraindications cannot be stated. We were unable to attribute any beneficial effect to its use in the cases of auricular fibrillation, short of that associated with maintenance of the ventricular rate within bounds.

The effect of theocalcin was observed in 1 case (case 2) on several occasions (table 1 and fig 2). The drug increased the cardiac output and the velocity of the blood flow and lowered the venous pressure, results similar to those previously recorded (Stewart and Cohn<sup>18a</sup>).

In case 3 a cure has apparently been obtained. The patient is well, without symptoms and signs, and is engaging in strenuous household duties. The measurements of the circulation have returned to normal (table 1 and fig 3). When the second pregnancy since operation occurred there was increase of the arteriovenous oxygen difference and decrease of the cardiac output. Continuation of pregnancy appeared to be contraindicated. There was restoration of normal circulatory measurements after therapeutic abortion (fig 3).

The speed of the circulation on the right and on the left side was studied by partition of the circulation time (table 3). There appeared to be no fixed pattern, the prolongation occurring on one side or the other or on both sides.

Three patients have been "cured," and the other 3 have been better since pericardiectomy (table 2). These results, though the number of cases is small, appear to be approximately the same as those recorded in the literature<sup>17</sup>. Analysis of the results favors the employment of pericardiectomy in the treatment of this syndrome.

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19 (a) Stewart, H. J., Crane, N. F., Detrick, J. E., and Thompson, W. P. Action of Digitalis in Compensated Heart Disease. *Arch Int Med* **62**: 547 (Oct.) 1938. (b) Stewart and Cohn<sup>18a</sup>. Stewart and others<sup>18b</sup>.

20 Cohn, A. E., and Stewart, H. J. (a) Evidence That Digitalis Influences Contraction of the Heart in Man, *J. Clin. Investigation* **1**: 97, 1924, (b) The Relation Between Cardiac Size and Cardiac Output per Minute Following the Administration of Digitalis in Normal Dogs, *ibid* **6**: 53, 1928, (c) The Relation Between Cardiac Size and Cardiac Output per Minute Following the Administration of Digitalis in Dogs in Which the Heart Is Enlarged, *ibid* **6**: 79, 1928.

The work of the heart was calculated by making use of the following formula <sup>21</sup>  $W = QR + \frac{wV^2}{2g}$ , in which W equals the work done per beat, Q equals the stroke volume, R equals the mean arterial blood pressure in millimeters of mercury multiplied by 136, V equals the velocity of the blood at the aorta, w equals the weight of the blood and g equals the acceleration due to gravity. The last part of the formula,  $\frac{wV^2}{2g}$ , has been omitted. The work of the left ventricle per beat was increased after operation in all except 1 case (case 6 [table 1])

TABLE 3—Data Relating to Velocity of Blood Flow (Circulation Time) in Five Cases of Chronic Constrictive Pericarditis

Case No	Date	Venous Pressure, Cm	Circulation Time				Comment
			A Arm to Tongue (Decholin Sodium), Sec	B Arm to Lung (Ether), Sec *	C Lung to Respiratory Center (Carbon Dioxide), Sec †	A Minus B, Sec ‡	
2	1/28/38	9.2	19.2	5.5	15.0	13.7	Cured after operation
4	1/29/38	18.8	21.5	13.5	9.5	8.0	Improved after operation
5	2/1/38	15.3	19.2	6.0	13.5	13.2	Improved after operation
6	1/28/38	15.5	21.4	8.3	12.0	13.1	Improved after operation
7	1/19/38	22.3	29.8	12.5	17.0	17.3	No operation
	2/5/38	7.3	25.9	11.0	14.3	14.9	No operation
	4/12/38	25.9	35.5		12.0		No operation
	4/19/38	8.1	27.7		12.0		No operation
	6/13/38	16.4	28.9		13.5		Operation on 5/26/38

\* Normal range, 3.5 to 8 seconds, average, 5.5 seconds (Hitzig, W. M. Am Heart J 10: 1080, 1935)

† This type of test was reported on by R. Gubner before the New York Heart Association on Feb 1, 1933

‡ The length of time recorded in column A minus that in column B should equal that in column C. The normal range is 4.5 to 9.5 seconds

The work of the left ventricle has not been plotted against the cardiac volume in these cases, since it was impossible to estimate how much of the cardiac shadow was due to thickening of the pericardium

#### SUMMARY AND CONCLUSIONS

An analysis of the clinical manifestations in 9 cases of chronic constrictive pericarditis has been given. In 7 of these cases partial pericardiectomy was performed. The presence of this syndrome should be considered when there are signs of congestive heart failure in the absence of the usual causes of failure. Three of the patients appear to be "cured," 3 others are greatly improved and the seventh is now convalescing from the operation. Our studies of the circulation have shown that this syndrome is associated with a decrease in the cardiac

<sup>21</sup> Starling, E. H. Principles of Human Physiology, ed 6, Philadelphia Lea & Febiger, 1933



output per minute and per beat, a rise in the venous pressure and a slowing of the velocity of the blood flow. These alterations are related to the obstruction to the flow of blood into the heart, that is to say, to interference with diastolic filling, and to the interference with contraction, by the thickened, adherent pericardium. With the institution of pericardial resection and the subsequent clinical improvement, the measurements of the circulation undergo parallel changes toward or to normal. There is parallelism in these cases between the clinical manifestations and the objective measurements of the circulation. Our experience in these cases leads us to recommend surgical treatment.

# ASCORBIC ACID IN BLOOD AND URINE AFTER ORAL ADMINISTRATION OF A TEST DOSE OF VITAMIN C

## A SATURATION TEST

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Numerous methods have been proposed for the determination of vitamin C deficiency and for the estimation of the degree of saturation of the bodily tissues with vitamin C. The majority of these methods involve measuring the amount of ascorbic acid excreted in the urine in twenty-four hours (1) while the subject is taking his usual diet and (2) after the administration of a test dose of vitamin C. These procedures necessitate the complete cooperation of the patient in order to avoid loss of part of the specimen, and there is difficulty in preserving the urine against oxidation, with resultant loss of vitamin C. For these reasons the methods are not applicable to ambulatory patients. The best single test of vitamin C nutrition is considered by many to be the determination of the amount of reduced ascorbic acid in the blood during fasting. It gives an indication of the degree of tissue saturation but not a complete one, as there may be fluctuations with daily variation in the quantity of vitamin C in the diet. The aim of this study was to find a method of determining the state of vitamin C nutrition which would be applicable to ambulatory patients, which would require only a few hours to perform and which would avoid some of the difficulties that have been enumerated.

We studied 22 persons (25 tests being performed): 3 normal adults, 6 persons with psychoneuroses, 8 with chronic diseases which were not etiologically related to vitamin deficiency, 2 with pellagra and 3 with evidence of multiple vitamin deficiency. A careful history in regard to diet was elicited from each person, attention being especially directed to the intake of vitamin C. In 3 cases in which a marked deficiency of ascorbic acid was found at the original examination, a second test was carried out subsequent to a period of treatment with

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vitamin C No patient with fever or an acute infectious process was included in this study

#### METHOD

A specimen of blood and one of urine were collected from the patient in the fasting state. Afterward 600 mg of ascorbic acid<sup>1</sup> was administered by mouth. Specimens of blood and urine were obtained at the end of one, three and six hours. Each specimen of urine included the entire amount voided after the time of the previous collection. Similarly, all urine passed from the sixth to the twelfth and from the twelfth to the twenty-fourth hour after the test dose was saved for examination. In a few instances a twenty-four hour specimen was collected the day prior to the administration of the test dose of ascorbic acid for comparison of findings. The urine was kept in dark, tightly stoppered bottles on ice and was acidified with glacial acetic acid (approximately 10 per cent by volume), these procedures having been shown to retard the oxidation of vitamin C. Day specimens were analyzed at once in most instances, always within two hours. One cubic centimeter of acidified urine, diluted with 10 cc of distilled water, was titrated against a solution of 2,6-dichlorophenolindophenol of such a concentration that 1 cc of the dye was equivalent to 0.02 mg of ascorbic acid. The quantity of urine in each of the specimens was measured, and the amount of ascorbic acid present was calculated. When the urine was highly colored, it was often necessary to dilute it with more than 10 cc of distilled water in order to obtain a definite end point. When a large amount of vitamin C was present in the specimen, dilution was first made, after which 1 cc of the diluted specimen was used in titration with the dye.

As a result of special observations we found that there was only a slight diminution in the amount of vitamin C in the urine if analysis was delayed for one or two hours when it had been collected as described, but after twenty-four hours the decrease at times amounted to 20 per cent or more. Similar findings have been reported by Abbasy, Harris, Ray and Marrack<sup>2</sup> and by Wright<sup>3</sup>.

The amount of reduced ascorbic acid in the blood plasma was determined by the method of Farmer and Abt<sup>4</sup>. Ten cubic centimeters of blood was collected in a tube containing oxalate and centrifuged immediately. Two cubic centimeters of plasma was transferred to another tube, to which was added 4 cc of distilled water and 4 cc of a 5 per cent solution of metaphosphoric acid. After further centrifugation, 2 cc of the supernatant fluid was titrated against a solution of 2,6-dichlorophenolindophenol of such a concentration that 1 cc of the dye was equivalent to 0.01 mg of ascorbic acid. The solutions of the dye (2,6-dichlorophenolindophenol) were prepared from tablets, each of which was equal to 1 mg of ascorbic acid. These were checked against freshly prepared solutions of ascorbic acid of known concentration and found to be accurate within the limits of experimental error of this method.

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1 The ascorbic acid used was supplied by Hoffmann-LaRoche, Inc., Nutley, N. J.

2 Abbasy, M. A., Harris, L. J., Ray, S. N., and Marrack, J. R. *Diagnosis of Vitamin C Subnutrition by Urinalysis*, *Lancet* **2** 1399, 1935.

3 Wright, I. *The Present Status of the Clinical Use of Cevitamic Acid*, *Am. J. M. Sc.* **192** 719, 1936.

4 Farmer, C. J., and Abt, A. F. *Determination of Reduced Ascorbic Acid in Small Amounts of Blood*, *Proc. Soc. Exper. Biol. & Med.* **34** 146, 1936.

A microburet reading to 0.01 cc was used in all titrations, the dye being titrated into the fluid being tested. The latter was placed in a white evaporating dish and a blue light used to facilitate determination of the end point, which was considered to be the first pink color lasting thirty seconds. All titrations were completed within two minutes. A distilled water blank value was determined, this value being subtracted from the final buret reading. Each titration was done in duplicate by each of two observers, and the average of these values was used in calculating the content of ascorbic acid in the specimen.

TABLE 1—*Vitamin C Content of the Blood and Urine*

Test No	Case No	Diagnosis	Dietary History of Vitamin C	Control, 24 Hour Out put in Urine, Mg	Blood (Fasting), Mg per 100 Cc	Vitamin C Content After Administration of 600 Mg of Ascorbic Acid				
						Blood, Highest Concentration, Mg per 100 Cc	6 Hour Output in Urine, Mg	Percentage of 24 Hour Out put in Urine	24 Hour Out put in Urine, Mg	Percentage of Test Dose Excreted
1	1	Hypovitaminosis	Very poor		0.05	0.31	0.95	88	1.08	0.2
2	2	Hypovitaminosis	Very poor		0.05	0.12	0.62	55	1.12	0.2
3	3	Hypovitaminosis	Very poor		0.06	0.20	0.49	17	2.86	0.5
4	4	Pellagra	Very poor	1.820	0.09	0.50	2.60	77	3.38	0.6
5	5	Rheumatic heart disease	Very poor		0.07	0.24	0.71	20	3.54	0.6
6	6	Epilepsy	Poor ?		0.21	0.86	3.07	75	4.06	0.7
7	7	Syphilitic heart disease	Very poor		0.17	0.64	0.83	7	4.45	0.7
8	8	Psychoneurosis	Poor		0.04	0.84	2.24	40	5.61	0.9
9	9	Psychoneurosis	Poor	10.670	0.19	0.47	2.80	41	6.87	1.1
10	10	Psychoneurosis	Fair		0.19	1.05	3.43	43	7.87	1.3
11	11	Normal	Fair ?	9.003	0.17	0.76	3.11	35	8.87	1.5
12	12	Psychoneurosis	Poor	6.150	0.21	1.15	3.97	41	9.55	1.6
13	13	Hookworm	Poor	9.240	0.52	1.71	3.46	36	9.63	1.6
14	14	Arteriosclerosis, allergy	1,050 mg in 21 days, poor previously		0.34	1.55	4.99	35	14.12	2.3
15	15	Mild pellagra	Fair		0.74	2.72	26.93			
16	16	Psychoneurosis	Fair		1.22	1.74	49.50			
17	2	Hypovitaminosis, after treatment	3,900 mg in 13 days	46.640	0.98	2.18	50.19	70	70.84	12.0
18	17	Psychoneurosis	Fair		0.43	2.32	70.49	85	82.70	13.7
19	18	Diabetes	Good		0.80	2.48	81.57	74	109.53	18.0
20	19	Chronic bacillary dysentery	Very good		0.82	2.99	48.59	41	116.31	19.0
21	20	Normal	Good	12.190	0.65	2.00	103.05	75	137.09	23.0
22	4	Pellagra, after treatment	4,500 mg in 15 days		1.61	2.48	136.05	75	179.70	30.0
23	21	Rheumatoid arthritis	Excellent		1.74	2.16	209.02	91	228.34	38.0
24	22	Normal	Excellent	17.800	1.38	2.97	109.73	45	240.40	40.0
25	3	Hypovitaminosis after treatment	3,500 mg in 9 days		1.93	2.60	180.16	62	291.15	48.5

## RESULTS

A number of pertinent findings made in the 25 tests which were performed are given in table 1. The results are listed in ascending order according to the amount of ascorbic acid excreted in the urine in twenty-four hours after the administration of the test dose. It may be seen that, in general, the better the dietary history in regard to vitamin C, the greater the output in the urine after the test dose. The amount of ascorbic acid excreted in six hours was calculated as well as the output in twenty-four hours, and the results were found to be

closely parallel. This observation will be discussed in detail later. The amount of reduced ascorbic acid in the blood during fasting likewise showed a close correlation with the previous dietary intake and also with the quantity of vitamin C excreted in the urine. The concentration of ascorbic acid in the blood reached higher levels after the administration of the test dose when the amount present during fasting was high. Little information regarding saturation of the tissues with vitamin C was obtained from examining the urine for twenty-four hours prior to the giving of a test dose of the vitamin except in 2 instances, 1 patient (case 4) showing extreme deficiency and another (case 2, test 17) a normal condition.

On the basis of the following considerations, the first 14 tests have been considered as indicative of vitamin C deficiency and the last 11 tests as indicative of a fairly normal state of nutrition. Abbasy, Harris, Ray and Marrack<sup>2</sup> have shown that for the normal person the minimal daily excretion of vitamin C in the urine in twenty-four hours is 13 mg and that after the administration of a test dose of 700 mg there is an excretion of 40 to 50 mg in the subsequent twenty-four hours. The first 14 tests, that is, those designated as indicating deficiency, fail to meet these criteria, while the last 9 tests, considered as indicating a normal condition, satisfy these requirements. Two patients (cases 15 and 16) were given only six hour tests but were placed in the group of normal patients for reasons which will be discussed later. Van Eekelen<sup>5</sup> has stated that when vitamin C is being administered daily in amounts varying from 250 to 400 mg, as saturation of the tissues is reached there is a definite rise in the urinary output of vitamin C (above 30 mg). Even with a single large dose of ascorbic acid, a urinary excretion of 70 mg or more in twenty-four hours, as shown in tests 17 through 25, seems significant of near saturation.

The last column in table 1 indicates the percentage of the test dose excreted in the twenty-four hours following its administration. Hawley and Stephens<sup>6</sup> found that saturated subjects excreted 40 to 100 per cent of an oral test dose of 100 to 200 mg in this period. Wright<sup>3</sup> stated that about 30 per cent of a test dose of 500 to 1,000 mg should be excreted in twenty-four hours and that an output of less than 20 per cent indicates suboptimal storage of vitamin C. Youmans<sup>7</sup> concluded that excretion of 30 per cent or more of a test dose of 600 mg is the lower limit of saturation. Using these criteria, the last 5, and

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5 Van Eekelen, M. On the Amount of Ascorbic Acid in Blood and Urine Daily Human Requirements for Ascorbic Acid, *Biochem J* **30** 2291, 1936

6 Hawley, E. E., and Stephens, D. J. Rate of Urinary Excretion of Test Doses of Ascorbic Acid, *Proc Soc Exper Biol & Med* **34** 854, 1936

7 Youmans, J. B., Corlette, M. B., Akeroyd, J. H., and Frank, H. Studies of Vitamin C Excretion and Saturation, *Am J M Sc* **191** 319, 1936

possibly the last 7, tests may be considered to indicate saturation and the preceding 2 near saturation

*Detailed Study of Urinary Excretion*—Examination of the specimen of urine obtained from the patient in the fasting state gave little and often misleading information. The content of ascorbic acid varied considerably both in the normal and in the deficient persons (table 2), and there was marked overlapping of findings. This confirms the view of a number of investigators that examination of a single specimen of urine is valueless.

TABLE 2—*Ascorbic Acid in the Urine After a Test Dose of Ascorbic Acid\**

		Output of Ascorbic Acid, Mg					
	Test No	During Fasting	1 Hr	1-3 Hr	3-6 Hr	6-12 Hr	12-24 Hr
Deficient persons	1	0.41	0.05	0.37	0.53	†	0.13
	2	0.14	0.25	0.16	0.21	0.24	0.26
	3	0.21	0.37	0	0.12	†	2.38
	4	0.46	0.30	0.78	1.52	†	0.78
	5	0.07	0.07	0.07	0.57	†	2.83
	6	2.27	0.43	1.14	1.50	†	0.99
	7	0.18	0.08	0.02	0.24	1.67	2.45
	8	0.63	0.29	0.67	1.29	1.03	2.34
	9	0.81	0.37	0.88	1.55	1.64	2.42
	10	0.41	0.33	1.02	2.08	1.11	3.33
	11	0.25	0.35	0.73	2.02	3.03	2.73
	12	0.17	0.47	1.10	2.42	3.19	2.40
	13	1.54	1.27	1.31	0.88	1.92	4.25
	14	0.18	0.32	1.27	3.40	6.61	2.52
Normal persons	15	0.07	0.22	12.29	14.42	†	†
	16	9.63	5.57	16.80	27.12	†	†
	17	†	2.14	20.64	27.40	12.84	7.81
	18	0.32	0.36	11.47	53.65	7.47	4.75
	19	0.06	0.79	16.49	64.31	20.17	7.76
	20	0.36	1.36	3.21	44.03	†	67.72
	21	1.07	0.53	18.24	84.28	28.52	5.52
	22	0.44	0.74	94.90	40.41	41.80	1.84
	23	1.94	5.45	112.07	91.50	11.41	7.90
	24	0.66	0.97	54.94	53.82	116.48	14.19
	25	1.72	3.14	54.27	122.75	50.24	64.75

\* The test dose consisted of 600 mg. of ascorbic acid.

† Included in the twelve to twenty-four hour specimen.

‡ No specimen was collected.

One hour after the administration of the test dose, all but 2 of the group of normal persons showed an increase in the amount of ascorbic acid in the urine, but in only 3 instances was it of significant degree (to 1 mg. or more). For the group of deficient persons there was a rise in only 4 tests, this increase amounting in each case to less than 0.3 mg. The urine which was collected between the first and the third hour after the administration of the test dose showed a marked increase in the quantity of ascorbic acid excreted by all normal persons, the amount varying from 3.2 to 112 mg. For the subjects who showed deficiency, there was no increase in the output of vitamin C in this period, or else the rise amounted to less than 1 mg. In the specimen collected between the third and the sixth hour after the test dose, the

quantity of ascorbic acid eliminated by normal persons ranged from 14.4 to 122.7 mg, for those who were deficient the quantity ranged from 0.12 to 3.4 mg. At the end of twelve hours the excretion of vitamin C continued to be increased for the normal persons but at a slower rate, and at the end of twenty-four hours the excretion had decreased almost to the level noted before the test dose was given.

For the subjects who were normal in regard to vitamin C, the rate of excretion per hour was greatest between the first and the third hour in 6 instances, varying from 1.6 to 5.6 mg, and between the third and the sixth hour in 5 instances, varying from 4.8 to 40.9 mg. The amount of ascorbic acid per cubic centimeter of urine was calculated throughout our investigation but was found to be an unreliable measure of the actual excretion, owing to wide variations in dilution and concentration, hence the total output in the urine during a given period should always be determined.

In summary, when vitamin C nutrition is normal, the response to 600 mg of ascorbic acid given orally is a marked rise in urinary excretion, beginning at the end of the first hour and reaching a peak some time between the first and the sixth hour, followed by a gradual decline, approaching the original level at the end of twenty-four hours. When the vitamin C stores of the body are deficient, there is no rise in the output of vitamin C in the urine, or an insignificant one, after the test dose.

#### PROPOSED SIX HOUR URINARY EXCRETION TEST FOR SATURATION

Since the greatest increase in excretion of ascorbic acid in the urine occurred during the first six hours after the administration of 600 mg of this substance, the total output in this period was calculated and compared with the amount excreted in twenty-four hours. In chart 1 the findings are shown graphically, the solid columns representing the six hour and the total columns the twenty-four hour excretions. It may be seen that when the excretion during the twenty-four hour period was high or low the same was true regarding the six hour period. In the group of normal persons from 41 to 91 per cent (average 61 per cent) of the total amount of vitamin C excreted in twenty-four hours was excreted in the first six hours (table 1), in the group of deficient persons from 7 to 88 per cent (average 44 per cent) was excreted. Hawley and Stephens<sup>6</sup> reported similar findings, using a test dose of 100 to 200 mg given by mouth. They found that saturated subjects excreted 55 per cent and depleted ones 47 per cent of the twenty-four hour output in the first six hours. In our series the actual amount of vitamin C eliminated in six hours after the administration of the test dose varied from 48.5 to 209 mg for the normal persons and from

0.3 to 4.9 mg for the depleted persons. When over 20 per cent of the amount of vitamin C administered was excreted in twenty-four hours (e. g., when the tissues were nearly saturated), the six hour output was above 100 mg. In 2 instances only a six hour test was performed. One patient (case 16) excreted 49.5 mg in this period, the other (case 15), who had pellagra, excreted 27 mg. The findings in each of these instances have been considered to represent normal nutrition. An output of 49.5 mg is comparable to that found in several tests of normal

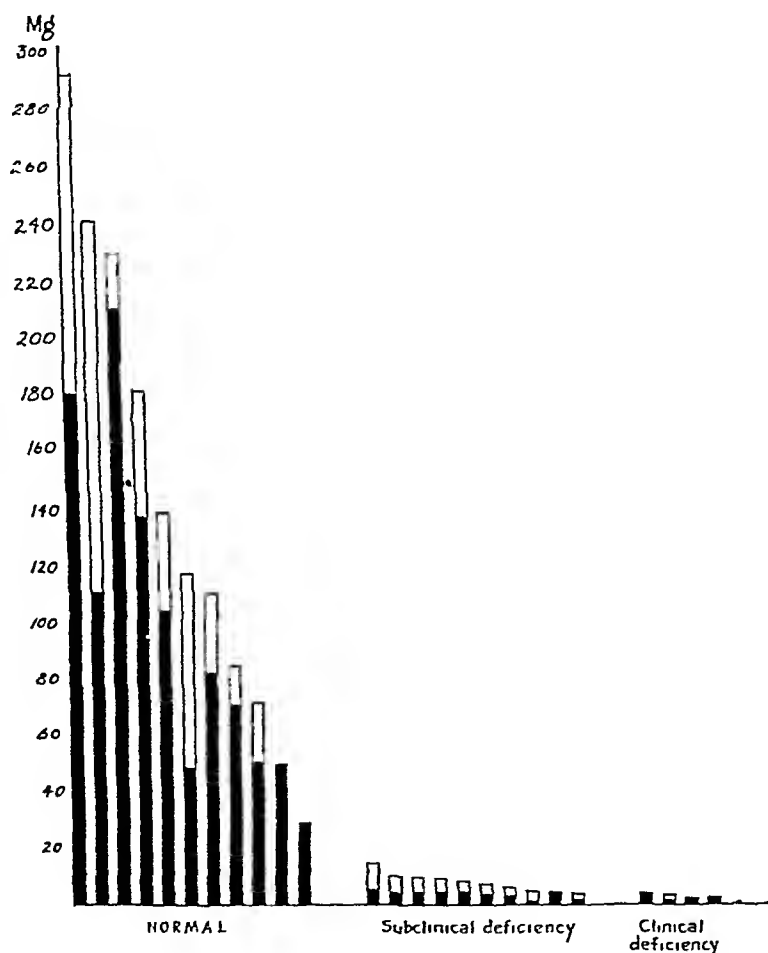


Chart 1—Urinary excretion of vitamin C after the administration of a test dose of 600 mg of ascorbic acid. The black columns indicate the six hour output, and the white columns indicate the twenty-four hour output.

persons. An excretion of 27 mg may indicate slight subnutrition, but examination of the blood in this case showed no evidence of deficiency.

In view of these findings, it seems that as much information can be obtained by examining the urine for the content of ascorbic acid excreted in six hours as by examining that excreted in twenty-four hours after the administration of a test dose of this substance. To test the vitamin C nutrition 600 mg of ascorbic acid may be given



by mouth and the urine collected for the subsequent six hours. If 50 mg or more is excreted, the person may be considered normal in regard to the ascorbic acid content of the body, while if over 100 mg is excreted, partial or actual saturation of the tissues is indicated. Excretion of less than 50 mg may be associated with depletion of the vitamin C stores of the body.

Harris and Abbasy<sup>8</sup> have recently proposed a simplified procedure to determine the state of vitamin C nutrition, in which the output of ascorbic acid is measured between the fourth and the seventh hour after the administration of a test dose of this substance. Our findings for a comparable period, between the third and the sixth hour, showed an output for the normal persons of from 27.4 to 122.7 mg (table 2), the amount excreted averaging 44 per cent of the total twenty-four hour excretion. By the depleted persons from 0.1 to 3.4 mg was excreted, the output averaging 23 per cent of the twenty-four hour excretion. Examination of the urine for this short interval after the test dose, during which the maximum increase in the excretion of vitamin C occurs, gave considerable information regarding the state of vitamin C nutrition.

#### ASCORBIC ACID IN THE BLOOD •

*In the Fasting State*—In our series of 25 tests the level of reduced ascorbic acid in the blood varied from 0.04 to 1.98 mg per hundred cubic centimeters (table 1). For the group considered normal according to findings obtained on examination of the urine, from 0.43 to 1.98 mg, with an average of 1.11 mg, of ascorbic acid was present per hundred cubic centimeters of blood, for the group considered deficient, from 0.4 to 0.52 mg, with an average of 0.17 mg, per hundred cubic centimeters. Six subjects showed less than 0.1 mg per hundred cubic centimeters, 4 of them exhibiting clinical evidence of vitamin deficiency. Normal blood values during fasting range from 0.65 to 2 mg per hundred cubic centimeters, according to various observers, figures above 1.3 mg being indicative of saturation.<sup>9</sup> Only 1 of the group

8 Harris, L. J., and Abbasy, M. A. A Simplified Procedure for the Vitamin C Urine Test, *Lancet* **2** 1429, 1937.

9 (a) Wright, I. S., Lilienfeld, A., and MacLenathan, E. Determination of Vitamin C Saturation: A Five Hour Test After an Intravenous Test Dose, *Arch. Int. Med.* **60** 264 (Aug.) 1937. (b) Pijoan, M., and Klemperer, F. Determination of Blood Ascorbic Acid, *J. Clin. Investigation* **16** 443, 1937. (c) Abt, A. F., Farmer, C. J., and Epstein, I. M. Normal Cevitamic Acid Determinations in Blood Plasma and Their Relationship to Capillary Resistance, *J. Pediat.* **8** 1, 1936. (d) Greenberg, L. D., Rinehart, J. F., and Phatak, N. M. Studies on Reduced Ascorbic Acid Content of Blood Plasma, *Proc. Soc. Exper. Biol. & Med.* **35** 135, 1936. (e) Van Eekelen.<sup>5</sup>

of normal persons showed less than 0.65 mg, presenting a value of 0.43 mg. This person's response to a test dose of vitamin C was normal as far as urinary excretion was concerned. The low value may have been due to a reduced intake of this vitamin for a day or two prior to the test, the diet previously having been adequate. This one finding indicates that occasionally a single determination of the ascorbic acid in the blood may lead to fallacious interpretation. Of the 4 persons with blood values above 1.3 mg per hundred cubic centimeters, which is considered the level of saturation, all excreted 30 per cent or more of the test dose in the urine in twenty-four hours (table 1) and 109 mg or more in six hours. The subjects showing values between 0.65 and 1.3 mg per hundred cubic centimeters, which is considered normal, excreted 12 to 23 per cent of the test dose in the urine in twenty-four hours and 48.5 mg or more in six hours. The patients with values of less than 0.65 mg per hundred cubic centimeters had an output of 0.2 to 2.3 per cent of the test dose in the urine in twenty-four hours and an output of less than 5 mg in six hours. There was 1 exception, the person previously mentioned who showed a blood level of 0.43 mg per hundred cubic centimeters during fasting excreted 13.7 per cent of the test dose in twenty-four hours and 70 mg in six hours. These figures show the close correlation between urinary and blood findings as indicative of normal or deficient vitamin C nutrition.

*After the Administration of 600 Mg of Ascorbic Acid as a Test Dose*—The blood was examined for the content of reduced ascorbic acid one, three and six hours after the oral administration of 600 mg of ascorbic acid (chart 2). At the end of one hour there was a rise in the concentration of ascorbic acid, this rise persisted or reached a peak at the end of three hours. After six hours had elapsed there was usually a slight fall in the amount of vitamin C in the blood. The curves resembled those for a dextrose tolerance test, as has been suggested by Greenberg, Rinehart and Phatak<sup>9a</sup>. These investigators obtained a maximum increase two to four and one-half hours after giving 6 ounces (177 cc) of orange juice. Taylor, Chase and Faulkner<sup>10</sup> administered 1 Gm of ascorbic acid and found that normal persons showed a rise in the concentration in the blood which reached a peak in one hour and subsided in five hours. In 1 case of scurvy the rise was delayed, reaching a maximum at three hours and remaining high for two hours longer. In our series, the group of normal persons (11 tests) showed a rise to a maximum of 1.7 to 2.9 mg of ascorbic acid per hundred cubic centimeters of blood. In all but 1 instance a height of 2 mg or more was attained. For the group of deficient persons (14 tests) the highest

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<sup>10</sup> Taylor, F. H. L., Chase, D., and Faulkner, J. M. Estimation of Reduced Ascorbic Acid in Blood Serum and Plasma. *Biochem J* **30** 1119 1936.

concentration varied from 12 to 17 mg of ascorbic acid per hundred cubic centimeters, a rise above 11 mg occurring in only 2 tests. In all but 3 instances the maximum concentration was reached one to three hours after the test dose was given. A delayed rise may be due to slow absorption from the gastrointestinal tract or to diminished excretion by the kidneys due to renal damage. One person who showed this type of curve had chronic bacillary dysentery, 1 had generalized arteriosclerosis with evidence of diminished renal function and a third was a normal adult in good health. In patients in whom disease of the gastrointestinal tract is interfering with absorption, vitamin C nutrition may be tested by administering ascorbic acid intravenously.

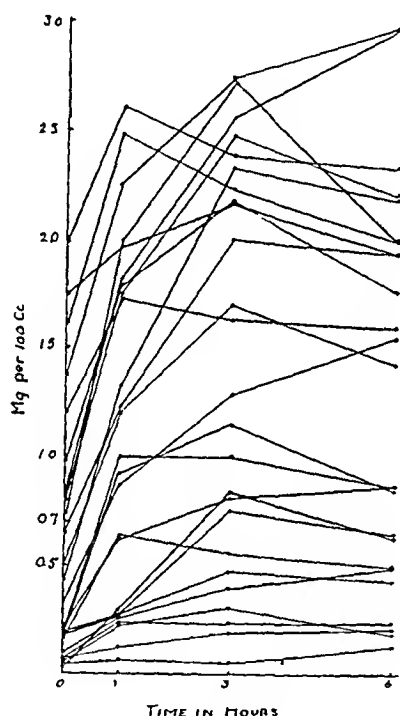


Chart 2—The reduced ascorbic acid content of the blood after a test dose of 600 mg of ascorbic acid

#### PROPOSED TEST OF THE BLOOD FOR VITAMIN C NUTRITION

The state of saturation of the tissues may be determined by examining the blood during fasting and one and three hours after the administration of 600 mg of ascorbic acid. An original level of reduced ascorbic acid of over 0.7 mg per hundred cubic centimeters, reaching 2 mg or more after the test dose, may be considered indicative of normal vitamin C nutrition. A value of over 1.3 mg per hundred cubic centimeters for the blood during fasting indicates tissue saturation. If the amount of vitamin C in the blood during fasting is less than 0.7 mg

and if it fails to rise to 2 mg or more at the end of three hours after the test dose, vitamin C deficiency is present

#### THE RENAL THRESHOLD OF VITAMIN C

The findings obtained on examination of the blood and of the urine showed a close correlation. When the level of ascorbic acid in the blood during fasting was high or when a high level was reached and

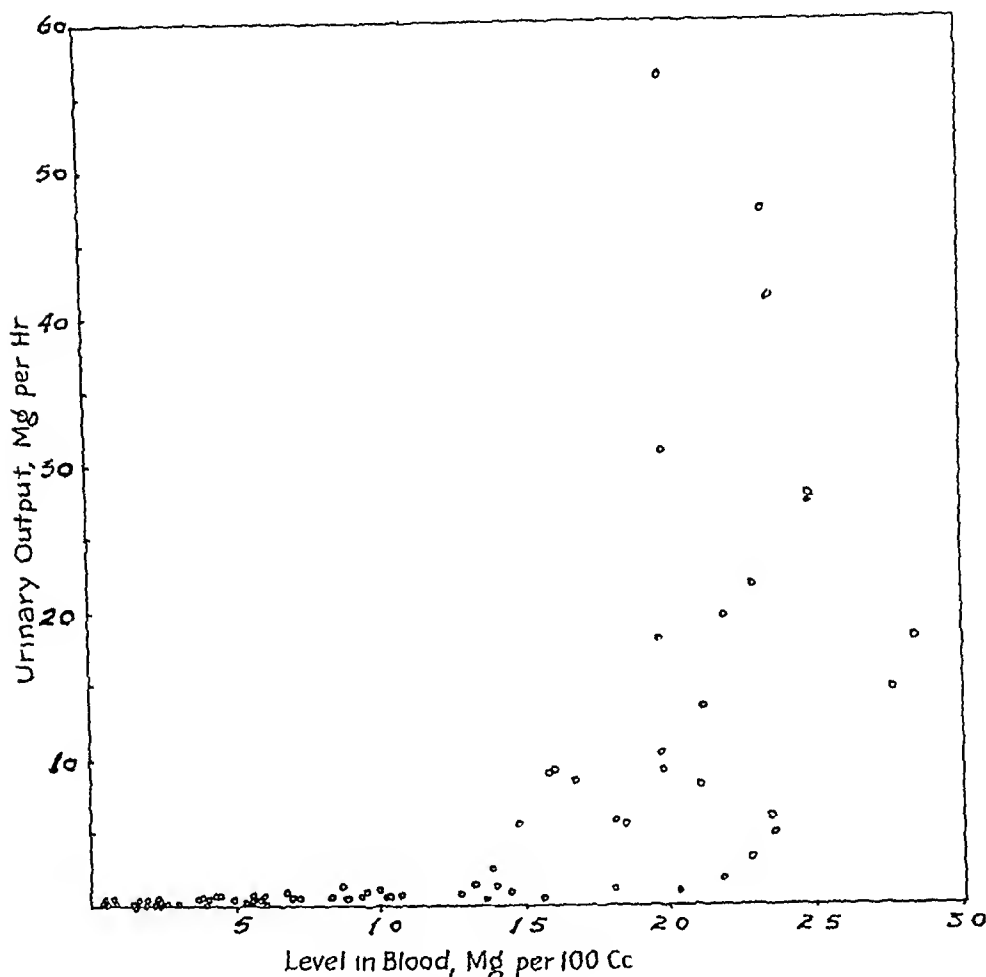


Chart 3—The relation between the amount of ascorbic acid in the blood and the amount excreted in the urine

maintained after the administration of a test dose, a large amount was excreted in the urine, when the quantity in the blood during fasting was low and when the rise was small, the urinary excretion was minimal. In chart 3 the amount of vitamin C excreted per hour in the urine is plotted against the concentration of ascorbic acid in the blood during the same period. The latter figure was obtained by averaging the concentration in the blood at the beginning and at the end of the particular period of urinary excretion. It can be seen that little vitamin C was

excreted by the kidneys until the level in the blood reached approximately 1.4 mg per hundred cubic centimeters, at which time an increase in the excretion of vitamin C occurred. Van Eekelen<sup>5</sup> has stated that when the level of ascorbic acid in the blood is greater than 1.3 mg per hundred cubic centimeters, the excretion in the urine is increased. Faulkner and Taylor<sup>11</sup> have reported a renal threshold of vitamin C in the neighborhood of 1.4 mg of reduced ascorbic acid per hundred cubic centimeters of blood.

#### STUDIES OF THREE PATIENTS WITH VITAMIN DEFICIENCY

Three patients who showed clinical signs of vitamin deficiency were studied at the time of admission to the hospital and after a period of treatment with vitamin C (table 1, tests 2, 3, 4, 17, 22 and 25). One of the patients had pellagra, with both cutaneous and gastrointestinal manifestations. Her diet had consisted of dried beans, rice, bread and coffee, with inclusion of meat and canned vegetables only once or twice weekly and citrus fruits about once a month. A second patient was originally considered as having a gastric neurosis, but it was subsequently shown that she was extremely deficient in vitamin C. For two months her diet had been extremely meager, containing small amounts of lean meat, rice and a few cooked vegetables, with no citrus fruits, tomatoes or cabbage. The third patient exhibited stomatitis, esophagitis, proctitis, vaginitis and evidence of loss of weight and dehydration. Her diet had been deficient for several months both in quantity and in quality, and she had never eaten citrus fruits or tomatoes to any extent. After the state of vitamin C nutrition had been tested, each of these patients was given 300 to 400 mg of ascorbic acid daily, and at the end of nine to fifteen days a second test was performed.

The results of the primary and subsequent tests are shown in chart 4. At the time of the original examination, after the administration of 600 mg of ascorbic acid, the urinary excretion was 1.1, 2.9 and 3.4 mg, respectively, of vitamin C in twenty-four hours, 0.5, 0.6 and 2.6 mg, respectively, being excreted in six hours. In other words, practically no ascorbic acid was excreted in the urine, as these small values may have been due to reduction of the dye (2,6-dichlorophenolindophenol) by other substances. The blood at this time showed during fasting 0.05, 0.06 and 0.09 mg, respectively, of ascorbic acid per hundred cubic centimeters. After the test dose the concentration rose to a peak of 0.12, 0.2 and 0.5 mg, respectively, per hundred cubic centimeters. After the period of vitamin C therapy and after the test dose the urinary excretion was 70.8, 179.7 and 291.1 mg, respectively, in twenty-four

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11 Faulkner, J. M., and Taylor, F. H. L. Observations on the Renal Threshold for Ascorbic Acid in Man, *J. Clin. Investigation* **17**: 69, 1938.

hours and 50.2, 136 and 180.2 mg, respectively, in six hours. The level of reduced ascorbic acid in the blood during fasting measured 0.98, 1.61 and 1.98 mg, respectively, per hundred cubic centimeters, rising after the test dose to 2.18, 2.48 and 2.6 mg, respectively, per hundred cubic centimeters. In other words, the vitamin C nutrition was normal, as judged by the examination of the urine and of the blood. From a clinical standpoint, all 3 patients were markedly improved. The gastrointestinal symptoms had cleared up in 1 case, the stomatitis, proctitis and vaginitis had disappeared in 1 case and the lesions of pellagra had nearly disappeared in the third case. The third patient was the only one to receive treatment other than vitamin C in addition to the ordinary hospital diet. She was also given large amounts of brewers' yeast daily.

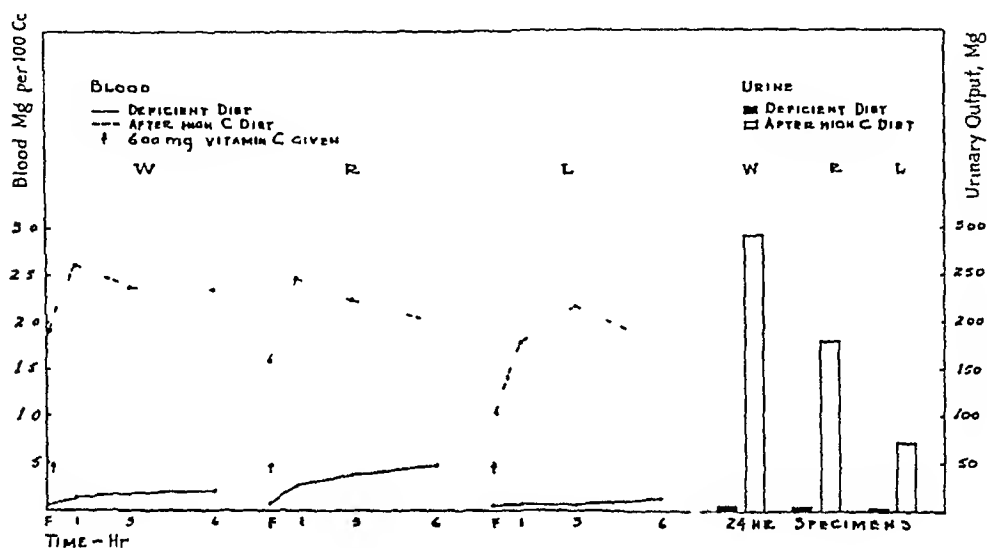


Chart 4—The ascorbic acid content of the blood and urine in deficiency states (3 cases) when the original diet was being taken and after a high intake of vitamin C.

Of the 2 patients in this series who had pellagra, 1 showed marked deficiency of vitamin C, as already described (table 1, case 4), the other, for whom only a six hour test of blood and urine was performed, revealed findings at the low limit of normal (table 1, case 15). It seems likely that when a person exhibits deficiency of one vitamin, there may be deficiency of other vitamins as well. States of multiple vitamin deficiency have been recognized with increasing frequency in recent years. A further study of the state of vitamin C nutrition in patients with pellagra is being undertaken. It is conceivable that some of the symptoms of this disease are due to lack of substances other than vitamin B<sub>3</sub> (or G), the pellagra-preventive factor.

## FREQUENCY OF VITAMIN C DEFICIENCY

Deficiency of ascorbic acid is a frequent finding in routine examination of patients in clinics and hospitals, as shown by Harris, Abbasy, Yudkin and Kelly<sup>12</sup> In this small series of 22 patients, of whom 17 were apparently normal clinically in regard to vitamin C nutrition, 14 showed evidence of deficiency with special testing Numerous vague complaints, such as fatigue, anorexia and indigestion, may be related to deficiency of this nutritive factor More definite disorders, such as stomatitis, vaginitis and proctitis, may be caused by an insufficient amount of vitamin C in the tissues of the body On the other hand, in view of the prevalence of subclinical vitamin C deficiency, caution should be used before attributing to ascorbic acid the role of an etiologic factor in any pathologic state A depletion of the vitamin C content of the tissues may be only a concomitant finding or a result rather than a cause of the disease which is being studied

## COMMENT

The results of this study and the findings of Harris and Abbasy,<sup>8</sup> previously mentioned, indicate that it is not necessary to measure the excretion of ascorbic acid for twenty-four hours after giving a test dose to determine the state of vitamin C nutrition Since this investigation was started, a short test has been reported by Wright and his co-workers,<sup>9a</sup> consisting of a study of urinary excretion for five hours after the administration of 1,000 mg of ascorbic acid intravenously The excretion of 400 mg in this period was considered to indicate normal nutrition Ralli, Friedman and Kaslow<sup>13</sup> have proposed the use of a three hour test of urinary excretion after the administration of 100 mg of vitamin C by vein, having found that normal persons excrete 40 per cent and depleted subjects 11 per cent of the injected vitamin in three hours The principle in each of these procedures is the same, the variants being the amount of vitamin C used as a test dose, the method of administration and the number of hours during which urine is collected A dose of 600 mg was chosen for our study because it was large enough to minimize the effect of reducing substances other than vitamin C in the urine and also to diminish the significance of the inherent error in the determination of the end point Similar amounts

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12 Harris, L J , Abbasy, M A , Yudkin, J , and Kelly, S Vitamins in Human Nutrition Vitamin C Reserves of Subjects of Voluntary Hospital Class, *Lancet* **1** 1488, 1936

13 Ralli, E P , Friedman, G J , and Kaslow, M Excretory Test for Vitamin C Deficiency and Subnutrition, *Proc Soc Exper Biol & Med* **36** 52, 1937

have been used in previous investigations, and an opportunity was afforded for comparison of results. The oral route is the simplest method of administration and is satisfactory in most instances, although occasionally findings may be inaccurate because of poor intestinal absorption. Van Eekelen and Heinemann<sup>14</sup> have suggested that intravenous administration or the use of large doses, over 300 mg., may simulate saturation. Erroneous conclusions may result if ascorbic acid is spilled into the urine, insufficient time being allowed for absorption by the tissues. Wright<sup>9a</sup> has stated that in order to avoid the danger of irregular intestinal absorption, ascorbic acid should be given by vein. In all examinations of the urine the presence of reducing substances other than vitamin C is a potential source of error. Van Eekelen and Heinemann<sup>14</sup> have indicated that this is especially true when the diet is high in protein or when diabetes is present. They have advocated removal of these reducing substances by precipitation with mercuric acetate. King,<sup>15</sup> however, has criticized this procedure because it introduces new sources of error. In choosing a method to determine the vitamin C nutrition and in evaluating the results, all these facts should be kept in mind. It is our opinion that for routine clinical use the administration of an oral test dose of ascorbic acid with examination of the urine excreted in a period of three or six hours is a satisfactory procedure.

Examination of the blood is free from much of the aforementioned criticism, and a saturation test dependent on estimation of the content of reduced ascorbic acid in the blood may prove to be more reliable than tests of the urine. Such a procedure has been suggested as a result of this study.

With the availability of methods which require only a few hours for their performance and which are applicable to ambulatory patients, an opportunity is afforded for studying large groups of persons, as a result of which the role of vitamin C in a number of pathologic states may be clarified.

#### SUMMARY

The state of vitamin C nutrition may be determined by measuring the excretion of ascorbic acid in the urine for six hours after the administration of 600 mg. of this substance. An alternative procedure consists in the determination of the amount of reduced ascorbic acid in the blood during fasting and at the end of one hour and of three

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14 Van Eekelen, M., and Heinemann, M. Critical Remarks on the Determination of Urinary Excretion of Ascorbic Acid, *J. Clin. Investigation* **17** 293, 1938.

15 King, C. G. Vitamin C, Ascorbic Acid, *Physiol. Rev.* **16** 238, 1936.



hours after the administration of a similar test dose. Criteria of normal vitamin C nutrition, of saturation and of depletion of the tissues are enumerated for each of these tests.

There is a definite relation between the level of reduced ascorbic acid in the blood and the amount of this substance excreted by the kidneys, when the former exceeds 14 mg per hundred cubic centimeters, urinary excretion increases.

Mild vitamin C deficiency is extremely prevalent, and too much importance should not be attached to depletion of the ascorbic acid content of the body in any disease.

# INTRAPERITONEAL PRESSURE DURING TREATMENT WITH ARTIFICIAL PNEUMOPERITONEUM

## A CLINICAL STUDY

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WAUWATOSA, WIS.

The purpose of this paper is to present a series of observations on the intraperitoneal pressure that was recorded during the course of pneumoperitoneum treatment of 91 patients with pulmonary tuberculosis. For measuring the intraperitoneal pressure the manometer of an ordinary pneumothorax apparatus, graduated in half centimeters, was used. The patient was in the supine position except when the needle was introduced by the subdiaphragmatic route, in which case he was lying on his side. In the overwhelming majority of instances the site of insertion of the needle was 3 fingerbreadths below and to the left of the umbilicus. When the subdiaphragmatic route was used the needle was inserted slightly above the costal margin. All manometer readings were taken during quiet respiration.

The initial treatment was always given by the subumbilical route. The intraperitoneal pressure at this point is, as a rule, neutral (atmospheric). There were only 7 patients for whom the initial reading was slightly negative, or subatmospheric. This can be explained by the fact that in rare instances the subdiaphragmatic pressure is transmitted as far as the subumbilical region. In another group of patients that I treated with pneumoperitoneum by the subdiaphragmatic route I found that under normal conditions the intraperitoneal pressure was negative in that area. The cause is the transmission of negative pressure from the corresponding pleural cavity.

An illustration of the changes in the intraperitoneal pressure following the injection of a gradually increasing amount of air is presented in the accompanying table. The graphs show that the same amount of air may elicit different degrees of rise in pressure in different persons. The factors that are responsible for this are (1) the variable tonicity and integrity of the abdominal wall, including the diaphragm, (2) the variable size of the abdominal cavity, (3) the variable status of the lung and pleura and (4) the presence or absence of peritoneal adhesions. The abdominal wall is likely to relax after the injection of air, to

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counteract the increased intraperitoneal pressure. This reflex accommodation on the part of the muscles of the abdominal wall has been recognized in many instances by the fact that there is a considerable drop in the manometer reading two or three minutes after the injection. Chart 1 illustrates this point. A steep, rapidly rising curve signifies a case in which readings were taken directly after the injection and the injections were continued immediately afterward. In instances in

*Maximum Direct Intraperitoneal Pressure*

Manometer Readings	Number of Treatments																
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
After injection of 500 cc of air	11	13	13	17	17	18	16	15	16	18	18	18	15	16	14	16	13
After injection of 1,000 cc of air	6	14	20	18	21	18	22	19	22	21	22	20	16	16	20	17	18
Prior to periodic refills		8	16	16	14	17	13	14	11	19	20	14	13	10	14	13	12

Manometer Readings	Number of Treatments																
	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	
After injection of 500 cc of air	18	14	16	18	19	13	13	14	13	14	16	17	18	13	20	14	
After injection of 1,000 cc of air	21	18	20	22	20	16	17	13	16	20	22	22	24	20	24	24	
Prior to periodic refills	17	10	14	15	15	18	14	12	15	16	17	17	20	15	15	20	

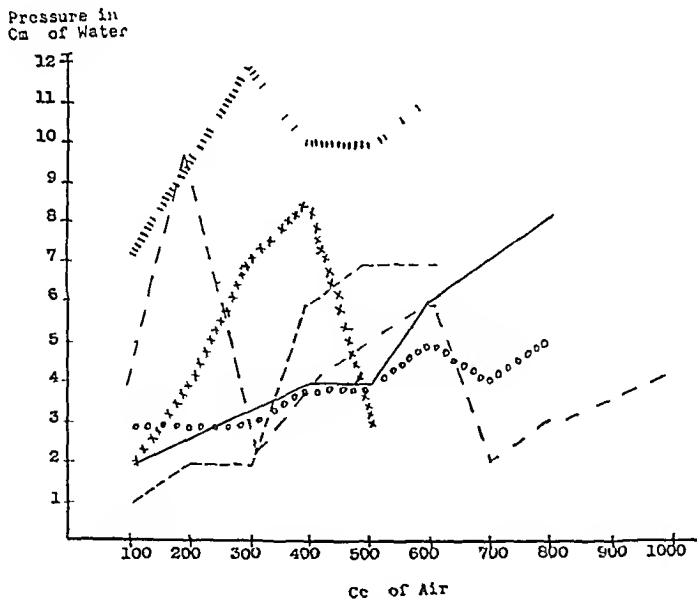


Chart 1—Changes in the intraperitoneal pressure after the injection of gradually increased amounts of air at the first treatment. Each curve indicates data for a different patient.

which some time was permitted to elapse between the reading of the manometer and the injection of air, there was a drop in pressure in spite of the additional amount of injected air. In 1 instance the pressure decreased by 8 cm of water. One must therefore consider two kinds of intraperitoneal pressure, (1) the direct pressure, observed immedi-

ately after the injection of air, and (2) the indirect or delayed pressure that registers after abdominal accommodation has occurred

The difference between direct and indirect intraperitoneal pressure is noticeable throughout the course of treatment. It is, however, less marked when pneumoperitoneum is well established than at the beginning of the treatment. I have made no attempt to determine the time necessary for the return of increased intraperitoneal pressure to normal. The greatest drop in pressure in a two minute period was 10 cm of water, it occurred after the injection of 800 cc of air at the fourth treatment. In no instance have I seen the pressure drop below 2 cm in two minutes. On the other hand, I have observed a return of the intraperitoneal pressure to the atmospheric level in a week, although it had been as much as + 5, + 9, + 11 and even + 14 cm at the completion of a previous injection a week before.

In contrast to this observation, I have had patients for whom a persistently positive manometer reading was noted at weekly intervals after the first injection throughout the course of treatment. There were 12 patients for whom positive pressure was noted only occasionally when weekly treatments were given. This group of patients included 6 who prior to the establishment of pneumoperitoneum had undergone surgical paralysis of the phrenic nerve (this operation may add considerably to the abdominal capacity) and 2 patients in whom flabbiness of the anterior abdominal wall allowed considerable distention after the injection of air. I have calculated that for 74 patients in whom a persistent positive intraperitoneal pressure was established an average of approximately 5,300 cc of air in six treatments was required to attain it. The average pressure at the sixth treatment in these cases was 3.8 cm of water.

The appearance of a positive intraperitoneal pressure at the time of periodic measurements does not necessarily mean the establishment of a constant positive pressure. I have seen a number of patients for whom positive readings were recorded at weekly refills prior to the injection of air on one or on several occasions but for whom the manometer registered atmospheric pressure for weeks subsequently. In most of these patients a persistent positive intraperitoneal pressure was finally attained. This phenomenon must be attributed to a prompt but limited accommodation by the muscles of the abdominal wall. In some patients a persistently positive level of pressure changed to a persistently atmospheric level when the general condition became very poor and the preterminal stage was reached. I wish to call attention to a few instances in which, after a prolonged period of positive manometer readings, an atmospheric pressure was noted on one occasion and was followed by continued positive readings on subsequent occasions. I am of the opinion that this unusual occurrence was not due

to a sudden drop in the intraperitoneal pressure but rather to faulty technic. It is probable that the end of the needle was blocked by some of the abdominal contents, most likely by the omentum or the intestinal wall.

Manometric oscillations corresponding to the two respiratory phases were commonly observed after the injection of moderate amounts of air. The usual range of oscillations was from 1 to 3 cm after injection of 500 cc of air, but a minimum oscillation of 4 cm and a maximum oscillation of from 5 to 9 cm were recorded in several cases. After

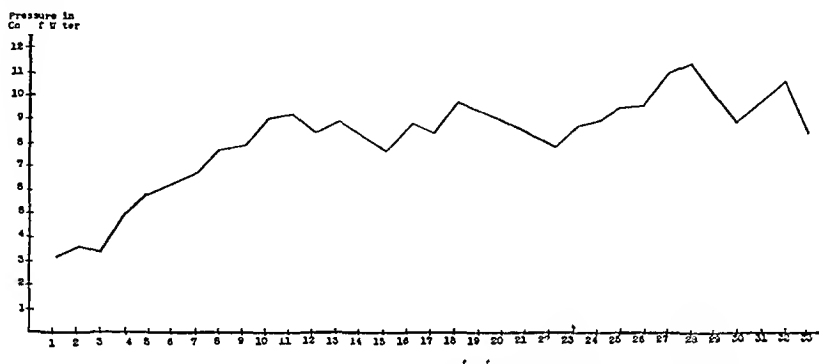


Chart 2—Direct intraperitoneal pressure after the injection of 500 cc of air

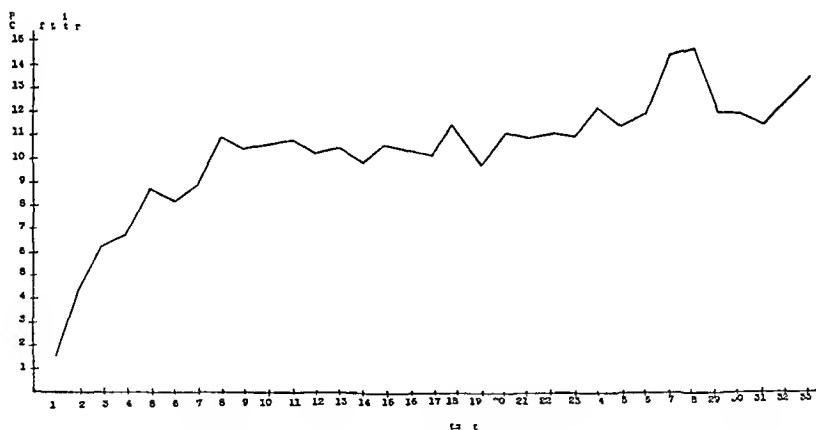


Chart 3—Direct intraperitoneal pressure after the injection of 1,000 cc of air

the injection of 1,000 cc of air the usual range of oscillations was from 1 to 4 cm, but it reached a maximum of 10 cm in some instances. At the time of the refills, a week after previous treatments, the usual oscillation was 1 cm, but it reached a minimum of 3 cm and a maximum of 7 cm occasionally.

Chart 2 indicates the average intraperitoneal pressure after the injection of 500 cc of air. It is to be noted that there is a slowly rising intraperitoneal pressure during the first few weeks, a plateau of approximately 9 cm of positive pressure is reached in about ten weeks,

one treatment a week being given, and the pressure remains at this level, with minor changes during the subsequent course of treatment. After the injection of 1,000 cc of air a level of 11 cm is reached in about eight weeks, one treatment a week being given. Although marked deviations from this level were observed in some cases, it can be seen that with moderate amounts of air injected at regular intervals it was possible to obtain a constant increased intraperitoneal pressure. This increased pressure was always compatible with the patient's comfort. Empiric observations have shown<sup>1</sup> that this increased intraperitoneal pressure was sufficient to cause a rise of the diaphragm, which, in turn, induced therapeutically adequate relaxation of the diseased lung. I<sup>2</sup> have demonstrated by roentgenographic measurements that increased intraperitoneal pressure can cause reduction of the apico-basal diameter of the lung to the extent of 32.8 per cent. The clearing of extensive parenchymal lesions and the closure of large or multiple tuberculous cavities, accompanied by the disappearance of toxic symp-

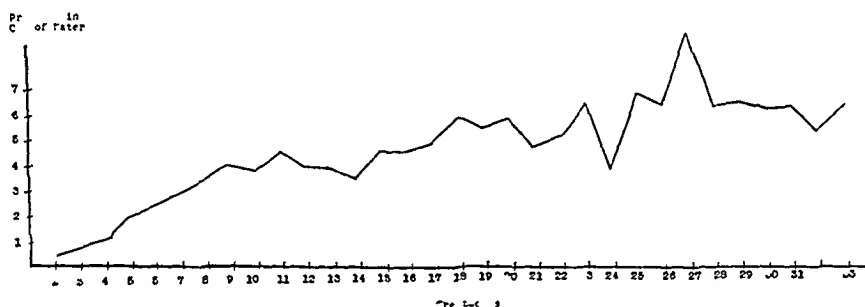


Chart 4—Direct intraperitoneal pressure prior to periodic refills

toms and by marked improvement in the general condition, were observed in several of the cases included in this study.

That the injection of 500 to 1,000 cc of air at weekly intervals is capable of maintaining an elevated intraperitoneal pressure is well illustrated by chart 4. This graph shows the average intraperitoneal pressure taken at weekly intervals prior to refills. It can be seen that from the ninth week (nine injections) the intraperitoneal pressure remains at + 4 cm or higher. This is brought about by replacement of the air absorbed from the abdomen by the blood stream and by introduction of more air into the peritoneal cavity than relaxation of the muscles of the abdominal wall is able to counterbalance.

For several of the patients, when the pneumoperitoneum was well established the treatments were continued by the subdiaphragmatic route instead of the subumbilical route used at the beginning of the

1 Banyai, A. L. *Pneumoperitoneum, Dis. of Chest* 30:8 (Dec.) 1937.

2 Banyai, A. L. *Radiological Measurements of the Apicobasal Relaxation of the Lung During Artificial Pneumoperitoneum Treatment*, *Am. J. M. Sc.* 196:207 (Aug.) 1938.

treatment The reason for this was that injection of air into the peritoneal cavity is easier by the subdiaphragmatic route The initial manometer readings are, as a rule, lower in this region than in the hypogastrium At the time of refill, following the injection of 500 to 1,000 cc of air, the manometer registers either a pressure less than that below the umbilicus at the time of the preceding observation or equal to it Transmission of the intrapleural negative pressure into the subdiaphragmatic air pocket caused substantial decrease in the manometer readings in some of the cases in this study These observations, however, must be qualified by recognition of the fact that the varying respiratory efforts of the patient may have caused differences in pressure

It is worthy of recording that for 1 of my patients, a 46 year old woman with far advanced pulmonary tuberculosis involving all the lobes, artificial pneumoperitoneum was discontinued after eleven weeks' treatment and was reestablished eight months later Manometric readings showed no indication that adhesions had caused diminution in the size of the potential peritoneal space It was also interesting to note that of the 20 patients in whom unilateral surgical paralysis of the phrenic nerve had been produced prior to pneumoperitoneum treatment, the manometer readings were unusually low before periodic refills for 14 and after periodic injections of 1,000 cc of air for 8 patients

#### CONCLUSIONS

Observations are presented to illustrate the changes in the intraperitoneal pressure during the clinical application of artificial pneumoperitoneum It is demonstrated that in spite of the accommodation by the muscles of the abdominal wall, including the diaphragm, injections of moderate amounts of air (500 to 1,000 cc) administered at regular intervals are capable of inducing elevation of the intraperitoneal pressure This sustained increase of intraperitoneal pressure is compatible with the patient's comfort and is conducive to therapeutically useful relaxation of the tuberculous lung

# A VARIABLE SYMPTOM COMPLEX OF UNDETERMINED ETIOLOGY WITH FATAL TERMINATION

INCLUDING CONDITIONS DESCRIBED AS VISCERAL ERYTHEMA GROUP (OSLER), DISSEMINATED LUPUS ERYTHEMATOSUS, ATYPICAL VERRUCOUS ENDOCARDITIS (LIBMAN-SACKS), FEVER OF UNKNOWN ORIGIN (CHRISTIAN) AND DIFFUSE PERIPHERAL VASCULAR DISEASE (BAEHR AND OTHERS)

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The medical literature contains descriptions of a condition characterized by all or many of the following features prolonged fever, polyarthritis, polyserositis, endocarditis, erythematous cutaneous lesions, nephritis, anemia and a remittent cachectic course, with a fatal termination months to several years after the onset. This variation in the characteristics and the unknown cause of the condition have resulted in the application of a great variety of names to this syndrome, depending on the symptom complex or pathologic lesion which most impressed each author. The purpose of this communication is to present a similar case with necropsy studies.

## REVIEW OF THE LITERATURE

The association of visceral lesions with diseases of the skin has long been recognized. The reports by Osler<sup>1</sup> in 1904 of 2 cases of "visceral manifestations of the erythema group of skin diseases" may be early descriptions of the condition under discussion. When case reports<sup>2</sup>

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1 Osler, W. The Erythema Group of Skin Diseases [cases 19 and 26], *Am J M Sc* **127** 1 (Jan) 1904.

2 (a) Mook, W H, Weiss, R S, and Bromberg, L K. Lupus Erythematosus Disseminatus, *Arch Dermat & Syph* **24** 786 (Nov) 1931. (b) Weidman, F D, and Gilman, R L. A Case of Acute Disseminated Lupus Erythematosus, Necropsy Disclosing Acute Endocarditis, But Not Tuberculosis, *Brit J Dermat* **43** 641 (Dec) 1931. (c) Rose, E, and Goldberg, L C. Visceral Lesions of Acute Disseminated Lupus Erythematosus, *M Clin North America* **19** 333 (July) 1935. (d) Keefer, C S, and Felty, A R. Acute Disseminated Lupus Erythematosus. Report of Three Fatal Cases, *Bull Johns Hopkins Hosp* **35** 294 (Sept) 1924.



of "lupus erythematosus with systemic or visceral lesions" are reviewed, syndromes are occasionally encountered which strongly resemble those in the 2 cases reported by Osler. Similar conditions have been found associated with erythemas other than lupus erythematosus<sup>3</sup> and with purpura<sup>4</sup>.

In 1911 Libman<sup>5</sup> first recognized the existence of a peculiar clinico-pathologic entity, which he and Sacks<sup>6</sup> reported on in 1924 as "a hitherto undescribed form of valvular and mural endocarditis" or "atypical verrucous endocarditis." Prolonged fever, serositis, arthritis, endocarditis, nephritis and, in 2 of the 4 cases, facial lupus erythematosus were the outstanding features. In 1932 Gross<sup>7</sup> presented the pathologic data on the heart in these cases, adding reports of 7 other cases. The relation of the so-called Libman-Sacks syndrome to dermatologic manifestations and to lupus erythematosus particularly has recently been discussed<sup>8</sup>.

Two instances of this symptom complex were reported by Tremaine<sup>9</sup> in 1934 as "subacute Pick's disease (polyserositis) with polyarthritis and glomerulonephritis" and by Christian<sup>10</sup> as examples of "long-continued fever with inflammatory changes in the serous and synovial membranes and eventual glomerulonephritis, a clinical syndrome of unknown etiology."

Recently Baehr, Klemperer and Schiffman<sup>11</sup> recorded 23 cases of disseminated lupus erythematosus associated with diffuse peripheral

3 McEwen, E. L. Erythema Multiforme. Report of a Case with Necropsy Findings and Deductions, *Arch Dermat & Syph* **13** 331 (March) 1926

4 Friedberg, C. K., and Gross, L. Nonbacterial Thrombotic Endocarditis Associated with Acute Thrombocytopenic Purpura, *Arch Int Med* **58** 641 (Oct) 1936. Baehr, G., Klemperer, P., and Schiffman, A. An Acute Febrile Anemia and Thrombocytopenic Purpura with Diffuse Platelet Thrombosis of Capillaries and Arterioles, *Tr A Am Physicians* **51** 43 (May) 1936

5 Libman, E., cited by Gross<sup>7</sup>

6 Libman, E., and Sacks, B. A Hitherto Undescribed Form of Valvular and Mural Endocarditis, *Arch Int Med* **33** 701 (June) 1924

7 Gross, L. The Heart in Atypical Verrucous Endocarditis (Libman-Sacks), in *Contributions to the Medical Sciences in Honor of Dr Emanuel Libman*, New York, International Press, 1932, vol 2, p 527

8 Belote, G. H., and Ratner, H. S. V. The So-Called Libman-Sacks Syndrome. Its Relation to Dermatology, *Arch Dermat & Syph* **33** 642 (April) 1936

9 Tremaine, M. J. Subacute Pick's Disease (Polyserositis) with Polyarthritis and Glomerulonephritis. A Report of Two Fatal Cases, *New England J Med* **211** 754 (Oct 25) 1934

10 Christian, H. A. Long-Continued Fever with Inflammatory Changes in Serous and Synovial Membranes and Eventual Glomerulonephritis. A Clinical Syndrome of Unknown Etiology, *M Clin North America* **18** 1023 (Jan) 1935

11 Baehr, G., Klemperer, P., and Schiffman, A. A Diffuse Disease of the Peripheral Circulation (Usually Associated with Lupus Erythematosus and Endocarditis), *Tr A Am Physicians* **50** 139 (May) 1935

vascular lesions and frequently polyserositis and endocarditis as instances of a "diffuse disease of the peripheral circulation" Friedberg, Gross and Wallach,<sup>12</sup> in 1936, discussed 4 cases of "non-bacterial thrombotic endocarditis associated with prolonged fever, arthritis, inflammation of the serous membranes and widespread vascular lesions"

#### ANALYSIS OF CASES REPORTED WITH POSTMORTEM DATA

It is evident that a complete review of all the cases reported of this symptom complex is impossible because of the lack of definitely established diagnostic criteria by which to determine which cases should be included. However, with most of the outstanding clinical and pathologic features accepted as criteria, selection was made of 17 cases with post-mortem data. Unfortunately the 23 cases described by Baehr and his associates<sup>11</sup> were not reported individually, necessitating their exclusion. Other observations,<sup>13</sup> sometimes without pathologic studies, showed occasional similarities, but these were not sufficient to warrant inclusion of the cases in this analysis. It is possible that certain features have been overemphasized or that extraneous syndromes have been included.

1 *Incidence*—This symptom complex is certainly not common, but it seems a fair assumption that most large hospitals at one time or another have had several patients with this type of disorder.<sup>7</sup> Cannon<sup>14</sup> has seen 3 patients with this symptom complex in private practice in two years and has stated that there have been 8 such patients at the New York Presbyterian Hospital during the past few years. The condition appears to have a marked predilection for females, as few typical syndromes occurring in males have been reported.<sup>6</sup> Sixteen of the 17 cases selected for analysis were of females between the ages of 8 and 48 years. The ages in 13 of the cases ranged between 19 and 37 years, and the average age was 26.2 years.

12 Friedberg, C. K., Gross, L., and Wallach, K. Non-Bacterial Thrombotic Endocarditis Associated with Prolonged Fever, Arthritis, Inflammation of Serous Membranes, and Widespread Vascular Lesions, *Arch. Int. Med.* **58**: 662 (Oct.) 1936.

13 Stokes, J. H. The Diagnosis of Disseminated Erythematous Lupus [case 3], *M. Clin. North America* **10**: 290 (Sept.) 1926. Thursfield, H. The Skin Affections Occurring in Bright's Disease, *Med.-Chir. Tr.*, London **83**: 221 (Aug.) 1900. Lancaster, L. On Eight Cases of Uraemic Eruption of the Skin, *Tr. Clin. Soc. London* **25**: 49 (Aug.) 1892. Keith, N. M., and Rowntree, L. G. A Study of the Renal Complications of Disseminated Lupus Erythematosus. Report of Four Cases, *Tr. A. Am. Physicians* **37**: 487 (May) 1922. Osler<sup>1</sup>, Rose and Goldberg,<sup>2c</sup> cases 1 and 2. Keefer and Felty,<sup>2d</sup> cases 2 and 3. Mook, Weiss and Bromberg,<sup>2a</sup> case 2.

14 Cannon, A. B., in discussion on Belote and Ratner.<sup>8</sup>

2 *Duration*—The duration of the symptom complex ranged from four and one-half to forty-eight months, averaging about eighteen months. Correlation of duration with severity and extent of pathologic lesions could not be demonstrated, some of the most severe lesions occurred in cases in which the clinical course could not be traced back farther than six months. There was a suggestion that nephritis was slightly less common in those cases in which the course was of shorter duration.

3 *Clinical Features*—The course of clinical events was sufficiently inconstant and atypical of other diseases so that the diagnosis was established only after a period of months, during which time other conditions were excluded. The onset was gradual and most often was characterized by arthralgia and fever. Less common chief complaints were of facial eruption, precordial pain, dyspnea, palpitation, malaise, weakness, loss of weight, chills, sweats, cough, sore throat and abdominal pain. After this, various signs of widespread disease gradually appeared, there was progressive weakness, despite remissions, with death occurring as a result of uremia, pneumonia, cerebral or cardiac accidents or less well defined conditions.

Articular manifestations were present at one time or another in all 17 cases. Sometimes migratory polyarthritis continued for months, with pain, stiffness, swelling and less commonly increased temperature of the affected part. Local change in color was rarely noted.<sup>15</sup> In a few instances there were late deformities, usually of the smaller joints of the extremities.<sup>16</sup> These manifestations did not seem to respond to the usual therapeutic measures.

Inflammation of the serous membranes of the pleural, pericardial and peritoneal cavities was of common occurrence. All 17 patients showed some evidence of pleuritis. The involvement of the serous membranes manifested itself by pain, friction rubs and signs of effusion. These occurred early or late in the illness. Of the friction rubs, the most frequently recorded were pericardial. Sometimes serositis was not discovered during life. In a few instances persistent abdominal pain remained unexplained after postmortem examination.<sup>12</sup> In 1 case the chronic peritoneal inflammation was sufficiently extensive to cause marked lymphatic and venous obstruction.<sup>2a</sup> It was common for signs of pulmonary involvement to be present for many months. Bronchopneumonia occurred occasionally during the course of the illness but was most frequent as a terminal condition.

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<sup>15</sup> Libman and Sacks.<sup>6</sup> Friedberg, Gross and Wallach.<sup>12</sup>

<sup>16</sup> Tremaine.<sup>9</sup> Friedberg, Gross and Wallach.<sup>12</sup>

All the patients except the 2 with symptoms of shortest duration<sup>17</sup> showed evidence of increasing anemia. Endocarditis occurred in 12 of the 17 patients. The clinical signs varied widely. In 1 case the only clues were persistent tachycardia and fever.<sup>6</sup> The most frequent findings were blowing apical systolic, rough precordial systolic or soft pulmonary diastolic murmurs, occasionally with thrills. Except for gallop rhythm and extrasystoles, arrhythmia was absent. Electrocardiographic changes were not constant, left axis deviation, tachycardia and low voltage were the most frequently reported.

Thirteen of the patients had erythematous lesions, and when these were severe they seemed to become manifest early in the course. Facial lesions, involving the nose and adjacent areas of the cheeks to produce a butterfly-shaped pattern, were the most common. This type of lesion was usually diagnosed as acute diffuse lupus erythematosus, but on several occasions the question was raised whether it might be some other form of erythema, such as erythema multiforme.<sup>8</sup> The erythema involved the hands, less frequently the rest of the extremities, occasionally the chest or back and rarely the palate and buccal membranes. The cutaneous eruptions were usually described as being diffusely red and painless. Sometimes they were bluish red, raised, indurated, bullous or atrophic, with extensive scarring and pruritus. If their occurrence was remittent, a dusky brownish discoloration of the skin sometimes developed at the site of the original lesion. Alopecia was mentioned in 3 cases.<sup>2a, c</sup> On several occasions initiation or exacerbation of the dermatitis followed exposure to sunlight or ultraviolet rays.<sup>2c</sup> There was mention of repeated severe sunburn or other forms of dermatitis in the past history of some of the patients.<sup>18</sup>

Crops of white-centered or red petechiae were present in 6 of the 12 cases in which there was endocarditis, the former variety occurring in 3 instances.<sup>15</sup> The most common location was on the conjunctiva, although rarely the petechiae were generalized.<sup>6</sup> Once, transient tender erythematous nodes on the digits (Osler nodes) were described.<sup>6</sup> In another instance small subcutaneous nodules, with no microscopic evidence of associated rheumatic fever, were present on the backs of the hands.<sup>12</sup> Purpuric spots, noted in 4 cases, usually appeared on the trunk or the extremities.<sup>17</sup>

Nine of the patients had nephritis, and nearly all the rest had symptoms and signs of disturbed renal function. Two of the patients died in uremia.<sup>19</sup> Two had the nephrotic syndrome.<sup>20</sup> The blood pres-

17 Rose and Goldberg<sup>2c</sup> Libman and Sacks<sup>6</sup>

18 Mook, Weiss and Bromberg<sup>2a</sup> Tremaine<sup>9</sup>

19 Libman and Sacks<sup>6</sup> Tremaine<sup>9</sup>

20 Belote and Ratner<sup>8</sup> Tremaine<sup>9</sup>

sure was moderately elevated in an occasional case. The spleen was reported enlarged at postmortem examination in 8 cases but was palpable ante mortem in only 3 of these <sup>2c, d</sup>. Signs of splenic infarction were noted once, <sup>6</sup> although pathologically infarction was demonstrated in 5 cases. In about a fourth of the 17 cases mention was made that the edge of the liver was palpable, from the costal margin to 8 cm below. Icterus was absent. There seemed to be no relation between hepatic enlargement and ascites.

In more than half the cases general adenopathy was noted. The lymph glands were slightly tender, they were not adherent to the skin, subcutaneous tissues or one another and were rarely greatly enlarged. The mucous membranes presented various abnormalities. In almost half the cases there was sore throat, with injection but no remarkable exudation. In several instances minute, pinpoint erosions or vesicles were present <sup>20</sup>. About a fourth of the patients showed pyorrhea or gingivitis. Rigidity of the neck with Kernig's sign was present in 2 cases, associated with a normal spinal fluid <sup>6</sup>. No abnormal mental state was noted. There was no clinical evidence of pancreatic, thyroid or other metabolic disease.

4 *Laboratory Data*—No mention was made of anemia in the 2 cases of shortest duration (five months or less), <sup>17</sup> except for these there was always progressive anemia, sometimes less than 2,000,000 erythrocytes per cubic millimeter being recorded, with a correspondingly low hemoglobin level and with blood smears typical of secondary anemia. Leukocyte counts varied from 1,400 to 30,000 cells per cubic millimeter. In only 3 cases was the leukocyte count fairly consistently below 5,000, being 1,400, 2,800 and 3,200, respectively <sup>2a, c</sup>. Several times mention was made that the leukocyte count did not rise above normal limits, despite a high temperature and signs of sepsis. Differential leukocyte counts and the appearances of the cells were not significantly changed. Estimations of the platelet count, bleeding and clotting times and clot retraction and the results of the tourniquet test were also within normal limits.

Repeated culture of the blood was made in every case, a wide variety of aerobic and anaerobic mediums being used. In 1 instance ten cultures were made over a period of eight months <sup>8</sup>. In all 17 cases culture of the blood was repeatedly sterile.

Various chemical analyses of the blood showed no significant changes except for an increased urea nitrogen content in the cases in which there was azotemia <sup>19</sup>. In 3 cases, in each of which there was impaired renal function, hypoproteinemia (4 Gm per hundred cubic centimeters), with reversal of the albumin-globulin ratio, was recorded <sup>16</sup>. Serologic studies were of no consequence. One patient showed an alternately

positive and negative reaction to the gonococcus complement fixation test,<sup>9</sup> another showed a repeatedly positive reaction to the Wassermann test, which did not change after intensive antisyphilitic treatment and which was not associated with a history or clinical evidence of syphilis.<sup>12</sup> Agglutination tests for *Bacillus typhosus* and paratyphosus A and B and *Bacillus melitensis* gave negative results.

Albuminuria, red or white blood cells and various types of casts were practically constant urinary findings. Patients with marked impairment of renal function exhibited progressive oliguria and fixation of the specific gravity, ranging from 1.013 to 1.018. In the only instance in which studies were made of the protein content of serous fluid, there were no significant findings.<sup>9</sup> Examination of the sputum, stool and spinal fluid and intracutaneous tuberculin tests were not of significance. One determination of the basal metabolic rate in 1 case gave a value of +7 per cent.<sup>2a</sup>

*5 Pathologic Data*—There were no pathologic features which were consistently present in every case except pleuritis.

(a) *Serous Membranes* The serous membranes seemed to be especially involved in this syndrome. Pleuritis, with or without effusion, was a constant feature. In addition, there were few cases in which changes in the pericardial or peritoneal membrane were not present. All stages of acute or chronic inflammation could be demonstrated. Fluid was most often present in one or both pleural cavities, in amounts of less than 500 cc. Ascites was somewhat less frequent, and pericardial effusions were rarely observed.<sup>6</sup> Apparently cardiac failure, renal impairment or hypoproteinemia played a minor role in the production of such effusions. Marked evidence of chronic inflammation was frequently observed. Thus there was sometimes obliteration of the pleural or pericardial spaces with fibrous tissue, occasionally accompanied by perisplenitis or perihepatitis. Several times the descriptions indicated that these adhesions were edematous and easily torn apart, showing a loose connective tissue, with plasma cells, lymphocytes and eosinophils infiltrating the area.<sup>16</sup> Chronic inflammation was occasionally limited to a small area, such as the upper portion of the abdomen, the mesenteric folds or the costophrenic angles.

Despite the frequent clinical indications of synovial involvement, pathologic studies of joints were rarely reported. In 1 case hypertrophy of synovial villi, subperiosteal bone formation and inflammation with perivascular infiltration of the surrounding tissue were reported,<sup>9</sup> while in another instance similar articular and extra-articular swelling was observed along with endothelial proliferation and a small amount of dirty yellow fluid containing giant cells and a few gram-positive

cocci<sup>12</sup> In the latter case there were spindle-shaped phalangeal deformities In another case there was moderate edema of the capsule of the right knee joint<sup>12</sup>

(b) Heart There were no constant pathologic changes in the heart The organ was usually enlarged, with varying degrees of muscle changes edema, lymphocytic infiltration, small hemorrhages, parenchymatous degeneration, acute degenerative myocarditis or sometimes replacement fibrosis In some cases the endocardium was smooth and without evident lesion At times the atypical verrucous endocarditis of Libman and Sacks<sup>6</sup> was mentioned These vegetations, usually larger than rheumatic changes, were grayish, pinkish or yellowish and verrucous, with a tendency to spread to the mural endocardium, papillary muscles, chordae tendineae and sometimes the auricle, usually the left These were unassociated with such evidences of rheumatic infection as Aschoff bodies In 2 of these cases all four valves were involved<sup>6</sup> In other cases there were smaller vegetations, the size of a pinhead, composed of thrombi with platelets, slightly covered with endothelium and without spread of the growth to the auricular or ventricular endocardium Exudative fibrinous deposits, fibrous thickenings and granular and hyaline changes in the valves have also been reported In none of the cases of endocarditis was there a marked inflammatory reaction of the valve, usually there were only small scattered areas of organization at the bases of the vegetations In several cases chronic valvular changes, questionably rheumatic, were noted<sup>12</sup> Culture of vegetations or heart blood was sterile except for the isolation of *Streptococcus haemolyticus*, *Staphylococcus aureus* and *Bacillus alcaligenes faecalis* from three large vegetations present in the case reported by Weidman and Gilman<sup>2b</sup> All 12 patients with endocarditis showed some change in the mitral valve, and the tricuspid and aortic valves were each involved in half the cases, frequently together

(c) Blood Vessels Minute vascular lesions in the systemic and sometimes in the pulmonic circulation were stressed in this syndrome by Baehr and his associates,<sup>11</sup> who postulated that a progressive process might have occurred from simple capillary dilatation and thrombus formation with endothelial proliferation to degenerating, necrotizing lesions in the walls Sometimes these changes were widespread In 9 of the 17 selected cases under discussion the vascular changes were prominent enough to be mentioned In 1 case the vascular lesions were considered typical of periarteritis nodosa<sup>12</sup> In others there was thickening of the walls of only a few arteries, as in the spleen or kidney, or there were hyaline or granular plugs with fibrosis and recanalization Sometimes all the coats of the vessel exhibited focal or diffuse necrosis,

destroying all semblance of a normal artery. Rarely, the veins showed medial degeneration with surrounding infiltration<sup>12</sup>. The cellular response to such changes was not unusual.

(*d*) Kidneys. In 9 of the 17 cases under discussion there seemed to be true glomerulonephritis, and in 7 there were renal vascular changes of sufficient severity to be mentioned in the reports. Both patients dying with azotemia<sup>19</sup> had vascular alterations and some renal infection, in addition to glomerulonephritis. There were 2 additional cases, not classified as cases of nephritic involvement, in which renal vascular changes were present<sup>15</sup>. In the remaining 6 cases there were unusual urinary findings for which only congestion, minute hemorrhages or parenchymatous degeneration could be demonstrated. Of the 2 patients exhibiting the nephrotic syndrome, 1<sup>9</sup> had glomerulonephritis with fatty droplets in the tubules and hyaline deposits in the basement membranes of the tubules, and the other<sup>8</sup> showed chronic pyonephritis with "tubular nephrosis". Subcapsular abscesses, from which staphylococci were usually isolated, were recorded in 4 cases<sup>21</sup>.

A distinct type of renal alteration, apparently dependent on vascular changes, has been described in connection with this syndrome by Baehr and his associates<sup>11</sup>. In 20 of the 23 cases reported, there were conspicuous renal vascular changes. Glomerular proliferation and thrombosis were present in 18 cases, and in 13 of these there was almost complete hyalinization of the glomerular capillaries without lipid or amyloid deposition, which they termed a "wire-loop" lesion. Glomerular hyalinization was not stressed in the 17 cases under discussion.

(*e*) Other Organs. Thirteen patients had pulmonary consolidation, and the remaining 4 exhibited congestion or partial collapse of the lungs. While the consolidation approached lobar extent in a few instances, in the majority of cases it was patchy and bilateral, presenting the usual picture of bronchopneumonia. The spleen was enlarged in 8 instances, in 5 cases being associated with infarction. Hemosiderosis, congestion and acute hyperplasia were usually present, and the capsule was occasionally thickened, sometimes with the edematous adhesions previously mentioned. Sepsis was present once<sup>20</sup>. There were likewise no characteristic changes in the liver: the weight was not remarkable, parenchymatous degeneration and congestion were common and thickening of the capsule was recorded 6 times. In a few cases focal necroses were present<sup>22</sup>. In most instances the lymph glands of the thorax or abdomen were somewhat enlarged, exhibiting various stages of acute and chronic inflammation. The enlargement was rarely massive, seemingly being

21 Weidman and Gilman<sup>2b</sup> Keefer and Felty<sup>2d</sup> Libman and Sacks<sup>6</sup> Tremaine<sup>9</sup>

22 Mook, Weiss and Bromberg<sup>2a</sup> Libman and Sacks<sup>6</sup> Tremaine<sup>9</sup>



due to edema<sup>2d</sup> The only lesions noted in the few cases in which the brain was examined were edema and degeneration<sup>16</sup> The rest of the autopsy data, including several reports of pathologic changes in the skin,<sup>2a,d</sup> were so varied that correlation was impossible

(f) Tuberculous Lesions Tuberculous foci were observed in 4 instances in an axillary node,<sup>2d</sup> in mediastinal and tracheobronchial nodes,<sup>6</sup> in tracheobronchial nodes and the lungs<sup>2a</sup> and in mesenteric nodes<sup>9</sup> Only the last lesion was described as "healed", the rest were caseous In none was there dissemination of infection, as far as could be determined

#### REPORT OF A CASE<sup>23</sup>

M A, a woman aged 26, was admitted to the Syracuse University Hospital on Nov 20, 1935, complaining chiefly of soreness in the chest and cough of four weeks' duration

*History*—The patient was born in Kansas and came to New York five years before admission to the hospital Her family history was not remarkable except that one grandmother died of valvular heart disease Her father was living but had "rheumatism", her mother, five sisters and four brothers were living and well The patient resided on a farm with her parents, she had been a clerk in a clothing store in a small community for the past four years As a child she had chickenpox, measles, pertussis, scarlet fever, pneumonia and some undetermined disease of the skin which resulted in scars on the left anterior wall of the chest In 1918 she had a mild attack of influenza In 1927 she was at home in bed for two months with painful swelling of the left leg, which she stated did not involve the joints She recovered without any apparent residual condition She denied having a venereal infection She said she slept eight hours each night, used no drugs, alcoholic beverages or tobacco, and took an emulsion of liquid petrolatum with agar and phenolphthalein daily as a laxative She had had no injuries, roentgen examination, operation or hospitalization, and the review of the systems showed essentially no abnormality prior to the present illness Her weight was 140 pounds (63.6 Kg) at the time of onset The catamema was not remarkable

The present illness began in the fall of 1934, with an indefinite attack of soreness of muscles and pain in the joints, involving the knees, ankles, wrists, shoulders, elbows, back and fingers This illness persisted as a chronic condition with occasional pains in the joints and increasing lassitude, but the patient was able to continue her work In July 1935 she complained of occasional pains in the joints, marked malaise and lassitude which forced her to bed She had a low grade fever, a temperature of 99 to 100 F On Aug 10, 1935,<sup>24</sup> she had a temperature of 99.4 F, a pulse rate of 112, a blood pressure of 118 systolic and 80 diastolic and a body weight of 129 pounds (58.6 Kg) The findings were not remarkable except for enlargement of the joints of the fingers, the chest was clear and the spleen was not palpable The hemoglobin (Dare) value was 65 per cent The urine showed albumin (1 plus), with an occasional pus cell and hyaline cast The

23 This patient was seen by us at the Syracuse University Hospital

24 The patient's history and the report on the examinations and course prior to her admission to the Syracuse University Hospital were supplied by Dr A N Curtiss

Wassermann test of the blood gave a negative reaction. Culture of the blood showed no growth, and there was no serum agglutination for *B. typhosus* and *Brucella melitensis*.

Her condition remained the same until September, when she became acutely ill, with a temperature varying between 101 and 102 F nearly every day and a pulse rate as high as 150. In November there were signs of enlargement of the heart, with cardiac failure. There was a loud friction rub in the left axilla, which changed to bronchial breathing and moist rales. For two weeks prior to entry the patient had a sore throat, enlargement of the glands of the neck and the axilla, a palpable spleen and stridorous breathing. For several days there was a cough, with small amounts of yellowish sputum, never blood streaked. The signs in the chest increased, and the liver became palpable 3 fingerbreadths below the costal margin. During this period the leukocyte count varied between 5,000 and 8,000, with a normal differential count. Serum agglutination tests for *B. typhosus*, *B. paratyphosus*, *Br. melitensis* and *Bacillus tularensis* gave a negative reaction. The reaction to the Wassermann test of the blood remained negative. Salicylates had been tried in large doses for over a month, without effect.

*Admission to the Hospital*—On Nov. 20, 1935, the patient was admitted to the Syracuse University Hospital. In addition to the history which has already been given, the patient complained of some recent loss of hearing and stated that in July 1935 she had a few severe night sweats just prior to going to bed. She had had moderate dyspnea during the past year. There was no history of chills.

*Physical Examination*—Physical examination on entry revealed a temperature of 102 F, a pulse rate of 112, a respiratory rate of 22 and a blood pressure of 138 systolic and 90 diastolic. The patient was well developed and fairly well nourished. She was lying quietly in bed, apparently acutely ill but in no discomfort. On the face there was an erythematous area, extending over the nose to the lower part of the cheeks. The skull showed no exostoses, the scalp was profusely covered with brown hair and there were no scars. The pupils were equal and regular and reacted to light and in accommodation. The external ocular movements were normal, the media were clear, the disks were normal, the retinas were not unusual, except for a few fine granular changes in the maculas, and the retinal vessels appeared rather thick for the patient's age. The ears and the nose were not remarkable. There was dilatation of the alae nasi with each inspiration. The teeth were carious, the tongue was coated brown, the throat was red and inflamed and the tonsils were small and fibrous. There was no rigidity of the neck. The thyroid gland was not palpable. There were enlarged, tender suboccipital and posterior cervical glands, more marked on the left, the axillary and inguinal glands bilaterally were enlarged and tender, being the size of a pea or larger. The thorax was symmetrically developed, with equal, rapid, shallow expansion. There were five scars about 1 inch (2.5 cm) long on the skin of the upper right side of the chest. The breasts were normal, with no masses. There was flatness to percussion in the left axilla, the base of the left lung and below the angle of the right scapula, the upper part of the left side of the chest anteriorly was hyperresonant. In the flat areas there were bronchial breathing, increased whispered voice sounds and increased tactile fremitus, there were crepitant rales at the base of the left lung. The heart was enlarged to the left, with the sounds fast and forceful but of regular rate, force and rhythm, there was a soft systolic murmur at the mitral area. The abdomen was distended and tympanitic, with the liver palpable 4 fingerbreadths and the spleen 3 fingerbreadths below the costal margin. There was slight tenderness in the

epigastrium There were no other masses or any evidence of fluid The extremities showed moderate wasting of the muscles, there was no peripheral edema The superficial reflexes were present and hyperactive, no pathologic reflexes were elicited, there was no clonus, and coordination and the vibratory sensation were intact The skin was emaciated and dehydrated, with no rash apparent except on the face, there were no petechial spots There was a small, red decubital area over the coccyx The vulva was normal, with no discharge, the Skene and Bartholin glands were normal The cervix was small, and it pointed in the center of the canal and showed normal mobility and no tenderness The fundus was normal, with second degree retroversion, but was freely movable and not tender In the adnexial regions there was no mass, thickening or tenderness

*Laboratory Examination*—At the time of entry laboratory studies revealed hemoglobin, 78 per cent (12 Gm), erythrocytes, 3,500,000, and leukocytes, 11,600 per cubic millimeter, with 82 per cent polymorphonuclear cells and the rest of the differential count normal The red blood cells were poorly filled The urine was brown, cloudy and acid, with a specific gravity of 1.022, albumin (4 plus), sugar (1 plus) and no acetone or diacetic acid There were numerous pus cells, hyaline and granular casts and red blood cells A serum agglutination test for B typhosus showed a reaction in low dilution only, probably of negligible significance Roentgen examination of the chest revealed increased markings in the right lung, with thickening of the right interlobar pleura, with no evidence of true massive consolidation The left lung showed opacity in the base, with loss of the cardiophrenic and costophrenic angles The cardiac shadow was increased in width, with the angles rounded The impressions of the roentgenologist were (1) pneumonitis with partial consolidation in the lower lobe of the left lung, (2) pneumonitis with partial consolidation in the lower portion of the upper lobe and in the middle lobe and slight invasion of the lower lobe of the right lung, (3) probable pericarditis with effusion and (4) possibly pleuritic fluid in the lower portion of the left lung

*Course*—The patient was given symptomatic treatment for the cough and the distention She took fluids well The next day she appeared more alert, with the dehydration diminishing and the distention entirely relieved The spleen was readily palpable, the pharyngitis was improved and the lymph nodes were less tender Salicylates were administered in large doses Two days after admission to the hospital there was little change in the roentgen appearance of the chest The patient felt much improved at the end of a week Her temperature had continued at approximately 99 F At this time a transfusion of citrated blood was given At the end of two weeks she was still improving, with the temperature normal and the intake and output of fluids good

On examination on the nineteenth day in the hospital the face was flushed, the cervical and axillary glands were large and not tender and were easily mobile under the skin, the inguinal and epitrochlear glands were not enlarged No petechiae were seen on the conjunctiva, mouth or skin about the neck or chest, however, the skin showed numerous diffuse, red, macular spots resembling rose spots There was dullness at the apex of the right lung anteriorly and at the base of the left lung posteriorly, there were bronchial breathing and bronchophony at the base of the left lung The heart beat was regular, with the apex in the fifth interspace at the midclavicular line, no murmurs were heard, but the second mitral sound was rather sharp When the patient was turned on her left side a soft mitral systolic murmur was heard, the pulmonic second sound was not accentuated The spleen was enlarged and firm, with a rather sharp edge, the edge of the liver was just palpable, the abdomen was soft and not dis-

tended There was a firm swelling in the region of the left sacroiliac joint, which was not red or especially tender The similarity of the course of the patient's illness to that of Osler's disease, Libman-Sacks disease, Baehr's disease and disseminated lupus erythematosus was suggested at this time by one of us (E C R Sr)

The next day the patient was moved into another room in order to be exposed to more sunlight Careful peripheral vascular studies were undertaken twenty-two days after her admission to the hospital Slight cyanosis was noted when the hands were in a dependent position, normal oscillometric curves were obtained for both arms and low amplitude curves for both legs There was palpable pulsation in all the vessels These observations were felt to represent general inanition and low pulse volume rather than obliterative vascular disease The following day a red area the size of a silver dollar over the right sacroiliac joint was incised, and a large amount of pus was removed Staph aureus was present

Four days after exposure to sunlight there was a marked increase in the intensity of the bluish red discoloration of the cheeks, and maculopapular, deep red areas the size of a pea appeared on the left buttock The following day there were scaly, red erythematous areas with whitish crusts on the lower lobe of the right ear The biopsy of a small gland from the neck revealed "chronic lymphadenitis" For several weeks her temperature had varied between 99 and 100 F, with the pulse rate between 86 and 104 and the respiratory rate between 18 and 24 Four weeks after her admission to the hospital, culture of nasal secretion was positive for diphtheria, but an epidemiologist could find no clinical evidence of diphtheria Culture of material from the throat was sterile A brother of the patient, who was visiting her, complained of a sore throat, he was found to have a red pharynx and large congested tonsils but no diphtheritic membrane, and culture of material from his nose and throat was sterile

Twenty-nine days after her admission to the hospital and nine days after her exposure to sunlight was increased, the thoracic condition was much improved, but she appeared drowsy and slightly disoriented and complained of pain in the legs Her temperature had risen to 105 F, the pulse rate was 136, the respiratory rate was 24 and the blood pressure was 108 systolic and 86 diastolic Her temperature continued to be elevated for three days, and during this period she had "nightmares and cried out in her sleep" She appeared frightened and despondent The glandular enlargement was disappearing, but the spleen was still palpable She was moved to a darker room Five weeks after her entry the temperature was varying between 100 and 103 F She appeared weaker, had no appetite, had occasional abdominal distention and complained of headache and other vague aches and pains Her weight had fallen to 100 pounds (45.4 Kg)

Six weeks after entry there were more cutaneous lesions, particularly on the back and the side of the neck, there were a few on the abdomen and several on the legs The lesions were not elevated, some were covered with scales and were a dusky copper color, about 1 cm in width and not painful Several were herpetic, and there was evidence of herpes of the lips The apex beat was outside the midclavicular line, no murmurs were heard, there were moist rales at the base of the left lung, and the liver and spleen were palpable Roentgen examination of the chest showed inflammatory change in the lower field of the left lung without displacement of the heart, and there was thickening of the interlobar pleura on the right side The patient had frequent emeses of dark fluid and was unable to retain any liquid by mouth Her temperature was normal, the pulse rate was 80 and the respiratory rate 20 The blood pressure

had fallen from the level on entry, of 138 systolic and 90 diastolic, to 90 systolic and 60 diastolic. The pulse rate had been varying between 80 and 130, with the high rate occurring during the episodes of fever.

Two days later the patient was failing rapidly, with labored breathing, tachycardia and muscular twitching of the arms, hands and head. There was acute distention, which could not be relieved by enemas. The patient seemed disoriented part of the time. The following day the muscular twitchings became pronounced, large, dry bronchial rales were heard over the entire chest, and the heart sounds became distant and rapid, almost fetal in character. The patient was weak, disoriented and incoherent. There was marked oliguria. Death occurred forty-three days after entry and approximately twenty-seven months after the onset of the illness.

*Further Laboratory Studies*—The patient showed secondary anemia on entry which persisted throughout her stay in the hospital (ten days after entry the erythrocyte count rose to 4,500,000 per cubic millimeter but two days before death it was 3,700,000). The leukocytes numbered 11,600 per cubic millimeter on her admission to the hospital. The following day the leukocyte count was 8,800, and it continued to fall, reaching 4,800 at the end of ten days. The count persisted at approximately 5,500 until the last week, when it rose slowly to 14,200 preagonally. The polymorphonuclear count varied between 60 and 83 per cent and the lymphocytic cells between 13 and 33 per cent. There was little change in the rest of the differential count. Smears showed continually a high percentage of nonfilamented polymorphonuclears, from 32 to 67 per cent, and there were many unclassified cells. Twenty-six days after her entry the hematologist reported as follows: "A number of examinations of the blood with various stains seemed to establish the fact that this patient had a few myelocytes and promyelocytes in the smears. On one occasion a myeloblast was noted. There was always a distinct 'left-shift,' with an increase in the percentage of nonfilamented polymorphonuclears. Normoblasts were present in fair number, although only 1 might be seen in the examination of several fields. The hematologic data suggested possible blood dyscrasia or irritation of the bone marrow by neoplastic invasion, infection or toxemia." During the period when the leukocyte count was low, leukocytosis could not be stimulated by intensive liver therapy. Nine per cent promyelocytes, myelocytes and metamyelocytes were present on December 27, seven days before death. The red blood cells showed moderate anisocytosis and poikilocytosis, and a rare cell showed diffuse basophilia. On December 9 the platelet count was 260,000 per cubic millimeter.

Repeated urinalyses continued to show albumin, granular casts and white and red blood cells. Repeated specimens of urine did not show Bence Jones protein. The Mosenthal test showed a range in specific gravity from 1.012 to 1.019, with 440 cc of urine per day and 400 cc per night. The urine showed no abnormality on culture. The phenolsulfonphthalein test showed 75 per cent excreted in two hours. The nonprotein nitrogen content of the blood varied between 33 and 40 mg per hundred cubic centimeters. Repeated culture of the stools revealed no organisms of the typhoid, paratyphoid or dysentery groups.

Repeated serum agglutination tests for typhoid, paratyphoid A and B, dysentery and undulant fever gave negative responses. Three cultures of blood were sterile. Blood was injected into a guinea pig, which died after two weeks; autopsy showed no lesion of any known organism. The tuberculin test gave a negative reaction at seventy-two hours. A cutaneous test for *Brucella abortus* gave a negative reaction at seventy-two hours. The blood serum showed no leptospiras or borrelias of the relapsing fever group by direct dark field exami-

nation or by animal inoculation. The Bunnell test for heterophile agglutinins gave a negative reaction. The gonococcus complement fixation test gave an anticomplementary reaction. The Wassermann tests of the blood of the patient, her father and her two brothers gave negative reactions.

Culture of material from the nose was repeatedly positive for diphtheria but showed no increase in hemolytic streptococci. On several occasions culture of material from the throat showed an increase in hemolytic streptococci. On December 17 culture of nasal secretion was reported as showing diphtheria, culture of material from the throat did not. The Schick test gave a positive reaction after seventy-two hours, with the control reaction entirely negative. A virulence test for diphtheria gave a negative reaction, and the final culture of material from the nose and throat gave negative results. The sputum showed no spirochetes, yeast cells or tubercle bacilli. Urethral and cervical smears did not contain gonococci. Three weeks after entry cutaneous sensitivity tests with ninety-three common protein antigens all gave negative reactions. The Friedman modification of the Aschheim-Zondek test gave a negative reaction.

The sedimentation rate (Cutler) when corrected for the anemia was still rapid, and this alteration persisted throughout the patient's stay. It increased as the illness progressed and at the end of four weeks was 21 mm in fifteen minutes and 31 mm in one hour. The blood sugar level during fasting varied between 62 and 81 mg per hundred cubic centimeters. The dextrose tolerance test revealed the following values for sugar in the blood and in the urine during fasting, 80 mg and 1 plus respectively, at one hour, 160 mg and 1 plus, at two hours, 117 mg and 1 plus, and at three hours, 100 mg and 1 plus. The serum showed the following values for protein, albumin and globulin, respectively 8.4, 3.4 and 5.0 Gm on December 10, 7.2, 2.8 and 4.4 Gm on December 14, 12.1, 5.2 and 6.9 Gm on December 18, and 8.8, 3.2 and 5.6 Gm on December 20. The cholesterol value of the blood was 151 mg per hundred cubic centimeters on December 11 and 103 mg on December 20. The calcium value was 8.0 mg on December 16 and 7.7 mg on December 20.

The basal metabolic rate according to the Du Bois method was +41 per cent on December 11, +41 per cent on December 14 and +35 per cent on December 17. On all these days the temperature ranged between 98.8 and 100.6 F and the pulse rate between 80 and 90. Roentgen examination of the long bones showed no pathologic condition except bilateral exostoses in the distal portion of the shaft of each fibula. The skull revealed no evidence of a pathologic condition in the vault, the frontal bones were not fused and the suture line was seen.

The electrocardiogram made on December 4 showed sinus rhythm, a rate of 110 per minute, no axis deviation, a PR interval of 0.14 second, a QRS of 0.06 second and an RT of 0.24 second. The chest lead (apex beat and left leg) was abnormal. There was low voltage in all leads, and the T wave was upright. On December 9 the findings were the same except that the RT interval was 0.22 second, the RT intervals of lead I and lead II were concordant and the rate was 100 per minute. These findings were interpreted as indicating sinus tachycardia and, because of the low voltage, probably some myocardial damage.

Examination of the spinal fluid on December 13 revealed clear, colorless fluid, 5 cells per cubic millimeter, all lymphocytes, a normal globulin value, 7.45 mg of chlorides per hundred cubic centimeters, and 42 mg of sugar per hundred cubic centimeters. The Wassermann test gave a negative reaction with both the cholesterolized and the noncholesterolized antigen. The colloidal gold curve was 1122332100 (mixture of curves of types 2 and 3), and the gum mastic test gave a positive reaction. One week later the Wassermann test of the spinal

fluid was anticomplementary. On December 22 the spinal fluid showed an increased globulin value (200 cells per cubic millimeter, chiefly lymphocytes with a few polymorphonuclears). The Wassermann test gave a negative reaction with both antigens, and the colloidal gold curve was 011125432 (type 3). Two days before death the colloidal gold curve was 011123321 (type 3), and the gum mastic test gave a positive reaction.

*Postmortem Examination*<sup>25</sup>—Postmortem examination revealed externally a few small, irregular, reddened, scaly, slightly elevated areas over the face, ears, back and anterior thoracic wall, a small amount of purulent drainage from the left eyelid, marked sordes in the mouth, three old, white, oblique scars over the right upper portion of the chest, a recent reddish scar along the posterior border of the left sternomastoid muscle, a deep ulcer with a reddish base on the left buttock, marked abdominal distention, slight edema of the ankles, and enlargement of the anterior and posterior cervical lymph nodes bilaterally, with no enlargement of the remaining external lymph nodes.

The peritoneal cavity contained approximately 400 cc of clear, yellow fluid. Fibrinous adhesions were present between the diaphragm, the liver and the spleen, those about the spleen being particularly dense. There was also marked adherence between the stomach, the transverse colon and the liver. The omentum was studded with numerous small, soft whitish areas the size of a pinhead. There were many fibrinous adhesions throughout all the coils of the small intestine, and there was marked edema of the large bowel about the splenic flexure. The lymph nodes in all portions of the mesentery were markedly enlarged and showed on section reddish areas of hemorrhage.

The spleen weighed 300 Gm. The capsule was markedly thickened and edematous. When the organ was sectioned the capsule fell off the splenic substance, which was softer and slightly more grayish than usual. The malpighian corpuscles stood out rather prominently. The liver weighed 1,910 Gm. The capsule was somewhat thickened and roughened. On section the parenchyma was pale yellow, with irregular red mottling. The pancreas was somewhat enlarged, firmer than usual, of irregular shape and densely adherent to the surrounding tissue. On section the main duct of the pancreas was filled with a cheesy-like material, apparently dammed up secretion. The kidneys weighed 310 Gm. The renal substance pouted slightly beneath the capsule, and the cortex was somewhat paler than usual and presented a "cooked" appearance. The capsules stripped easily. The aorta was smooth and showed a minimal amount of yellowish thickening.

The remainder of the gastrointestinal tract, the appendix, the gallbladder and bile ducts, the adrenal glands, the organs of the pelvis and psoas muscle showed nothing unusual.

The right pleural cavity was almost completely obliterated by old and fresh fibrous and fibrinous adhesions. In the left pleural cavity, encapsulated in a pocket, was approximately 400 cc of clear, yellow fluid. The remaining surface of the left lung also showed numerous adhesions. The left lung weighed 380 Gm and the right 420 Gm. The lower lobe of the left lung was partially collapsed, deep reddish blue and doughy. The remaining portions of both lungs showed pulmonary edema, with numerous patchy areas which exuded fluid on pressure. The bronchi were reddened over their entire surface. The mediastinum,

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<sup>25</sup> Postmortem examination was performed at the Syracuse University Hospital on Jan 2, 1936, by Dr Robert O Gregg.

the mediastinal lymph nodes, the bronchial lymph nodes, the pulmonary artery (opened in situ) and the pulmonary vessels in the lungs showed nothing unusual

The pericardial cavity contained approximately 25 cc of clear, amber fluid. There was one area of dense, firm adherence between the visceral and the parietal pericardium on the anterior surface of the heart, covering an area measuring approximately 5 by 5 cm. The pericardial fat was markedly edematous. The heart weighed 370 Gm. On section the myocardium was deep reddish brown and firm. The auricular appendages, the tricuspid, pulmonary, mitral and aortic valves, and the coronary arteries showed nothing unusual.

The brain weighed 1,160 Gm. The dura was less adherent to the calvarium than usual, and the pia-arachnoid was somewhat thickened, particularly about the angle between the cerebellum and the pons. There was an increased amount of cerebrospinal fluid, which was slightly turbid. On section the substance of the brain was softer, and the vessels throughout were more prominent than usual. The base of the skull, the middle ears, the pituitary gland and the thyroid gland showed nothing unusual.

Section of the sternum and ribs showed a reddish gray, hyperplastic marrow, and there were a few reddened areas in the sternal marrow, apparently due to hemorrhage. Section of the femur revealed a markedly thickened cortex and a marrow cavity not much larger in diameter than an ordinary pencil. Spicules of bone were seen extending through the marrow cavity, and this marrow appeared hyperplastic. The synovial membrane of the knee joint was smooth and light gray.

A swab from the gallbladder did not show pus or organisms, and culture yielded no growth in forty-eight hours. Culture of blood from the right ventricle (one flask, undoubtedly contaminated) yielded *Staphylococcus albus* and diphtheroid bacilli.

Microscopic examination<sup>26</sup> of the sections made post mortem revealed the following data: rib—hyperplasia of the marrow cells, marrow from the femur—moderate hyperplasia of the entire cellular structure, pancreas—a diffuse infiltration by polymorphonuclear leukocytes and necrosis of the superficial fat, without evident hemorrhage, thyroid gland—alveoli dilated and lined by low flattened cuboidal epithelium, with focal areas of hyaline degeneration scattered throughout, adrenal gland—no evident lesion other than the infiltration of a few lymphocytes and monocytes on the peritoneal surface, pituitary gland—without evident lesion, ovary—graafian follicles conspicuously absent, lymph node—a moderate degree of edema and inflammatory reaction, brain—without evident lesion, choroid plexus—without evident lesion, spleen—no noteworthy lesion, liver—considerable fatty infiltration throughout the parenchyma, with no evidence of pigment retention, kidney—moderate chronic glomerulonephritis, with recent embolic manifestations, lung—an old organized caseating tubercle with the surrounding alveoli free from the inflammatory process, bronchus—a few foci of round cell infiltration just beneath the mucous membrane, mesentery—an occasional lymph follicle showing edema and an inflammatory reaction and considerable fat necrosis but no evidence of tuberculosis, skin—slight cornification of the surface epithelium, a moderate degree of atrophy of the corium, only a rare hair follicle and an occasional sweat gland, voluntary muscle—without evident lesion.

*Anatomic Diagnosis*—The anatomic diagnosis was (1) chronic and subacute polyserositis with pleuritis, pericarditis and peritonitis, (2) acute nephritis, (3)

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26 Dr A S Giordano, of South Bend, Ind, made this examination



acute pancreatitis, (4) slight adhesive meningitis, (5) splenomegaly with perisplenitis, (6) hepatomegaly with perihepatitis, (7) fatty infiltration of the liver, (8) pleural effusion, (9) bilateral pulmonary edema, (10) old organized caseating pulmonary tubercle, (11) ascites, (12) diffuse dermatitis, (13) generalized lymphadenitis, (14) hemorrhage and hyperplasia of the bone marrow, (15) thickening of the cortex of the femur and growth of bone in the medullary cavity, and (16) focal hyaline degeneration of the thyroid gland

The microscopic sections were also compared with those made for the 2 patients reported on by Tremaine<sup>9</sup> and by Wolbach,<sup>27</sup> who stated that the liver showed peculiar delicate cellular adhesions corresponding closely to those seen in the patients reported on by Tremaine

#### SUMMARY OF CASE REPORT

A 26 year old woman had a progressive cachectic illness of twenty-seven months' duration, characterized by the gradual onset of polyarthritis, malaise and remittent low grade fever, followed by pleuritis with effusion, pericarditis with effusion, myocardial failure, pharyngitis, generalized lymphadenopathy, hepatomegaly and splenomegaly, erythematous eruption of the face, left buttock, right sacroiliac region and right ear, nephritis, meningitis, ascites, and peritonitis

Laboratory studies revealed progressive secondary anemia, hyperplasia of the bone marrow, moderate leukopenia, albumin, pus, red blood cells, hyaline and granular casts in the urine, an increased erythrocyte sedimentation rate, low levels for calcium and cholesterol in the blood, a slightly elevated serum protein content, with a reversed albumin-globulin ratio, electrocardiographic evidence of sinus tachycardia and low voltage, an elevated basal metabolic rate (+ 35 to + 41 per cent), and abnormal findings for the spinal fluid, with an increased number of cells, an increased globulin content, a low sugar level, a type 3 colloidal gold curve and a positive gum mastic curve. Additional bacteriologic, chemical and serologic studies of the blood, bacteriologic and chemical studies of the urine, feces, sputum, spinal fluid and nasal and pharyngeal secretions, and roentgen examinations of the long bones and the skull were not remarkable

Pathologic examination showed diffuse lesions of the skin, generalized lymphadenitis, chronic and subacute polyserositis with pleuritis, pericarditis and peritonitis, ascites, pleural effusion, hepatomegaly and splenomegaly, fatty infiltration of the liver, focal hyaline degeneration of the thyroid gland, acute nephritis, acute pancreatitis, bilateral pulmonary edema, an old organized caseating pulmonary tubercle, hemorrhage and hyperplasia of the bone marrow, adhesive meningitis and thickening of the cortex of the femur, with growth of bone in the medullary cavity

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27 Wolbach, S B    Personal communication to the authors

# *A Variable Symptom Complex of Undetermined Etiology with Fatal Termination, Essential Clinical Laboratory and Pathologic Features in Eighteen Cases \**

Authors	Case Number	Sex	Age, Years	Duration of Illness, Mo	Joint Manifestations (Arthritis or Arthralgia)	Pleuritis	Abnormal Urinary Findings	Anemia	Pleural Effusion	Pneumonia	Pericarditis	Peritonitis	Endocarditis	Lymphadenopathy	Lupus Erythematosus	Nephritis	Pharyngitis	Arteritis	Splenomegaly	Perisplenitis	Petechiae	Perihepatitis	Hepatomegaly	Splenic Infarct	Purpura	Tuberculosis	Alopecia	Erythemas Other Than Lupus Erythematosus	Leukopenia	Joint Deformity	Azotemia	Swift Neck (Kernig Sign)	Nephrotic Syndrome	Meningitis	Pancreatitis	Elevated Basal Metabolic Rate	
Labin and Sacks <sup>9</sup>	1	F	10	1½	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Rose and Goldberg <sup>-c</sup>	4	F	27	5	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Mook, Weiss and Bromberg <sup>-a</sup>	3	F	45	1½	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Lilman and Sacks <sup>9</sup>	1	F	24	6	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
	2	F	37	9	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
	3	M	19	9	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Weidman and Gilman <sup>2b</sup>	3	F	19	9	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Friedberg, Gross and Wallach <sup>1c</sup>	1	F	21	11	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Tremaine <sup>9</sup>	2	F	32	12	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Belote and Ratner <sup>8</sup>	F	8	14	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Keefer and Felty <sup>2d</sup>	1	F	36	24	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Mook, Weiss and Bromberg <sup>2a</sup>	1	F	32	24	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Friedberg, Gross and Wallach <sup>1c</sup>	2	F	18	38	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Tremaine <sup>9</sup>	1	F	19	42	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Rose and Goldberg <sup>2c</sup>	3	F	25	48	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Total (17 cases)					17	17	17	17	15	13	13	12	12	10	10	9	9	9	9	8	6	6	5	5	5	4	1	3	3	3	3	3	2	2	2	0	0
Reifenstein, Reifenstein and Reifens	F	26	27	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Total (18 cases)				18	18	18	18	16	16	14	11	13	12	11	11	10	10	9	9	9	7	6	6	6	5	4	5	3	3	3	3	2	2	2	1	1	1

\* The reports of 17 of the cases were collected from the literature, and 1 case is reported in the present paper  
 † Slight

## COMMENT

The accompanying tabulation of the essential features in the 17 selected cases revealed that every patient exhibited articular manifestations and pleuritis, all but 4 pericarditis, pneumonia or some erythema, and all but 5, peritonitis or endocarditis. Slightly more than half had nephritis or more or less diffuse arteritis. Other findings were too varied to be of possible diagnostic value. There seemed to be no one pathologic process which could be demonstrated as responsible for the widespread lesions. On the contrary, the impression was gained from the bronchopneumonia, diffuse congestion and degeneration that the majority of the acute lesions were the result of terminal infection occurring after some unknown process had damaged the endothelial tissues, heart, kidneys or other organs, perhaps rendering them more susceptible to terminal sepsis. It is possible also that some of the pathologic processes that occurred during the prolonged course of many of the cases subsided with little or no residual evidence to be found post mortem.

Our patient was observed for twenty-four days after the diagnosis of "diffuse peripheral vascular disease associated with lupus erythematosus and glomerulonephritis" was made, during which time extensive studies failed to reveal any etiologic factor. It is interesting to note the marked increase in the severity of the cutaneous lesions and of the state of the illness following exposure to sunlight. Such phenomena have been recorded in other cases.<sup>28</sup> In the case presented, bacteria were demonstrated in four instances: (1) an increased number of hemolytic streptococci in the throat, (2) *Staph aureus* in the furuncle on the buttock, (3) nonvirulent diphtheria bacilli in the nose and (4) bacilli in the old caseating tubercle in the lungs. There was no evidence of widespread tuberculosis, which makes it difficult to conceive of the tubercle bacilli as responsible for the clinical picture. Tuberculosis has been suggested as the cause of lupus erythematosus, but recently there has been a tendency to minimize the finding of tubercle bacilli in these cases.<sup>29</sup> It seems reasonable to consider the tubercle in the case described as incidental and to look on the other bacteria present as secondary invaders. Nevertheless, infection with an unknown organism or organisms is a plausible explanation for a majority of the clinical signs and pathologic features. The involvement of the meninges is consistent with the apparent predisposition of the symptom complex to involve the serous membranes. Other abnormalities, such as the acute pancreatitis, the elevated metabolic rate and the low calcium and cholesterol levels of the blood, rendered the diagnostic problem all the more baffling.

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28 Mook, Weiss and Bromberg<sup>2a</sup> Rose and Goldberg<sup>2c</sup> Tremaine<sup>9</sup>

29 O'Leary, P. A. Disseminated Lupus Erythematosus, *Minnesota Med* 17 637 (Nov.) 1934

A symptom complex therefore presents itself which has no definite diagnostic criteria, no known etiologic factor and no single name by which it is designated. Most of the names by which it has been described are objectionable because they directly or by connotation emphasize certain features which have not been found to be universally present. This hampers the conception of the symptom complex as a possible unity and impedes progress toward a better understanding of the syndrome. To obviate this difficulty it is suggested that similar cases in the future be considered as a group, so that their various peculiarities may be given equal consideration but not undue prominence.

#### SUMMARY

The medical literature contains descriptions of a variable symptom complex which has all or many of the following features: prolonged fever, polyarthritides, polyserositis, endocarditis, erythematous cutaneous lesions, nephritis, anemia and a remittent cachectic course, with a fatal termination months to several years after the onset.

Reports of 17 such cases, with postmortem examinations, collected from the literature were analyzed. No definite diagnostic criteria could be adduced, although every patient exhibited articular manifestations and pleuritis, all but 4, pericarditis, pneumonia or some erythema, and all but 5 peritonitis or endocarditis. Slightly more than half had nephritis or more or less diffuse arteritis. Other findings were too varied to be of possible diagnostic value.

An additional case of our own, with postmortem data, is reported in detail. This patient showed most of the features that have been mentioned and also adhesive meningitis, acute pancreatitis, an elevated basal metabolic rate, lowered levels of calcium and cholesterol in the blood and hyperplasia of the bone marrow, which have not been previously described. Extensive studies gave no clue to the etiologic agent.

It is suggested that in the future similar ill defined conditions be considered as a group, in order that clarification may be aided.

NOTE—Since this paper was submitted, reports of several additional cases have been published which come within the scope of this symptom complex. The first patient<sup>30</sup> was a woman aged 29 years. Her illness, of approximately sixteen months' duration, was characterized by weakness, loss of weight, cough, arthralgia and cutaneous lesions, by a purpuric tendency which was only temporarily ameliorated by splenectomy, and by terminal myocardial failure, lymphadenopathy, pneumonia and nephritis. Pathologic examination disclosed in almost every organ multiple arterial lesions which were said by Dr. Tracy B. Mallory

30 Acute Disseminated Lupus Erythematosus, Periarteritis Nodosa, Cabot Case 24201, *New England J. Med.* **218**: 838 (May 19) 1938.

to be typical of periaarteritis nodosa. However, Dr Soma Weiss and several other clinicians contended that the clinical diagnosis should have been acute disseminated lupus erythematosus. The reader is referred to the excellent discussion of this case.

The second patient,<sup>31</sup> a girl of 12 years, exhibited during the four month course of her illness remittent fever, pyuria and anemia, with terminal myocardial failure, bronchopneumonia, pleural and pericardial effusions, cutaneous facial eruption and convulsions. Necropsy revealed hydropericardium, bronchopneumonia, hemolytic streptococcic empyema and septicemia and some embolic nephritis. Vascular lesions were not prominent. This case is of interest in that the clinical and pathologic diagnosis was acute disseminated lupus erythematosus, although cutaneous lesions were absent until three days ante mortem. In the discussion, reference was made to 15 cases reported from the Massachusetts General Hospital in which no constant lesion was observed post mortem.

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31 Acute Disseminated Lupus Erythematosus, Hydropericardium, Cabot Case 24341, *New England J Med* **219** 273 (Aug 25) 1938

# MENINGOCOCCIC SEPTICEMIA

## REPORT OF FIVE NEW CASES

ROBERT W HEINLE, M D

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Meningococcic septicemia can no longer be regarded as a rare disease. Its recognition has been increasingly frequent since Gwyn, in 1898, demonstrated meningococci in the blood stream and since the report of Salomon,<sup>1</sup> in 1902, of meningococcic septicemia which persisted for eight weeks. The disease may be divided into the acute fulminating and the chronic septicemic type, the latter with various metastatic lesions and with or without meningitis.

Acute fulminating meningococcic septicemia is invariably fatal. Cases have been reported<sup>2</sup> in which the patient died a few hours after the onset, with an extensive purpuric rash, hematemesis and tarry stools. As in other fulminating infections, some patients<sup>3</sup> have shown massive hemorrhage into the adrenals. These acute attacks are characterized by their abrupt onset, with chills and high fever, rapid progression, purpura and massive hemorrhage into many organs. There is no effective treatment.

Chronic meningococcic septicemia is observed more frequently. It is characterized by headache, purpuric cutaneous rash, arthropathy of greater or lesser severity and fever, which may resemble that of tertian or quartan malaria and in any event is frequently of the "picket fence" variety, with frequent regular chills. There is moderate leukocytosis.

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From the Department of Medicine, Western Reserve University School of Medicine, and the Lakeside Hospital.

1 Salomon, H. Ueber Meningokokkenseptikame, Berl klin Wchnschr **39** 1045, 1902.

2 Middleton, R., and Duane, W. Fulminating Meningococcus Septicemia Without Meningitis, Am J M Sc **177** 648, 1929. Burton, J. A. G., and Chalmers, D. K. M. Purpura as a Sole Sign in a Case of Meningococcal Septicemia, Lancet **1** 296, 1930.

3 Foucar, F. H. Acute Fulminating Meningococcus Infection with Bilateral Capillary Hemorrhage of the Adrenals as the Most Striking Gross Pathologic Lesions. A Case Report, Ann Int Med **9** 1736, 1936. Boone, J. T., and Hall, W. W. Meningococcal Septicemia with Report of a Case Showing Organisms in the Direct Blood Smear, U S Nav M Bull **33** 446, 1935.

The spleen may or may not be palpable. Numerous authors<sup>4</sup> have commented on the fact that positive blood cultures may not be obtained until after the third week and have stressed the necessity of employing mediums enriched with ascitic fluid or blood. The duration of the disease may be several months, cases in which it lasted three,<sup>5</sup> four,<sup>6</sup> five,<sup>7</sup> seven<sup>8</sup> or eight<sup>9</sup> months having been reported. Spontaneous recovery frequently occurs. Cases<sup>10</sup> in which terminal meningitis followed a long period of septicemia have been observed.

The less common manifestations of chronic meningococcic septicemia include involvement of many different organs. Acute and subacute meningococcic endocarditis have been reported. Gwyn<sup>11</sup> reported a patient with an eight month history of subacute bacterial endocarditis, proved at autopsy. Herrick,<sup>12</sup> in 31 autopsies, observed acute tricuspid endocarditis once, and other authors<sup>13</sup> have reported vegetative and ulcerative endocarditis. Myocarditis, with lesions resembling those of rheumatic fever, also has been reported.<sup>14</sup> Fibrinopurulent and sero-purulent pericarditis are known to occur.<sup>12</sup>

Meningococcic abscess of the sphenoid, frontal or ethmoid sinuses<sup>15</sup> has been reported. In Gardiner's case<sup>16</sup> metastatic iridochoroiditis

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4 (a) Appelbaum, E. Chronic Meningococcus Septicemia, *Am J M Sc* **193** 96, 1937. (b) Carbonell, A., and Campbell, E. P. Prolonged Meningococcemia. Report of Three Cases, *Arch Int Med* **61** 646 (April) 1938.

5 Pontano, T., and Trenti, E. La setticemia meningococcica, *Policlinico (sez. med.)* **29** 3, 1922.

6 Netter, A. Fievre intermittente se prolongeant cent deux jours. Nature meningococcique soupçonnée, *Bull. Soc. med. d. hôp. de Paris* **47** 46, 1923.

7 Graves, W. R., Dulaney, A. D., and Michelson, I. D. Chronic Meningococcemia, *J. A. M. A.* **92** 1923 (June 8) 1929.

8 Dock, W. Intermittent Fever of Seven Months' Duration Due to Meningococcemia, *J. A. M. A.* **83** 31 (July 5) 1924.

9 Goundry, F. W., and Phalen, T. H. Meningococcemia Without Meningitis, *New York State J. Med.* **37** 491, 1937.

10 Vesell, H., and Barsky, J. Chronic Meningococcus Septicemia, *Am J M Sc* **179** 589, 1930. Gutland, G. L., and Logan, W. R. Prolonged Meningococcemia with Terminal Meningitis, *Brit. M. J.* **1** 687, 1925.

11 Gwyn, N. B. Subacute Meningococcal Endocarditis, *Arch. Int. Med.* **48** 1110 (Dec.) 1931.

12 Herrick, W. W. The Intravenous Serum Treatment of Epidemic Cerebrospinal Meningitis, *Arch. Int. Med.* **21** 541 (April) 1918.

13 (a) McMahon, H. E., and Burkhardt, E. A. Meningococcic Endocarditis, *Am J Path.* **5** 197, 1929. (b) Rhoads, C. P. Vegetative Endocarditis Due to Meningococcus, *ibid.* **3** 623, 1927.

14 Saphir, O. Meningococcus Myocarditis, *Am J Path.* **12** 677, 1936. Rhoads<sup>13b</sup>.

15 Herrick, W. W. Extrameningeal Meningococcic Infections, *Arch. Int. Med.* **23** 409 (April) 1919.

16 Gardiner, A. W. A Case of Generalized Meningococcus Infection. *Brit. M. J.* **2** 1176, 1928.

developed, resulting in blindness Epididymitis<sup>41</sup> and empyema<sup>15</sup> also have been observed

Some arthropathy appears at one time or another during the course in nearly every case, varying from mild fleeting pain in a joint to actual destruction of bone Suppurative arthritis, however, is uncommon Gardiner<sup>16</sup> reported suppurative arthritis of a knee joint in 1 case, from which meningococci were cultured, and Dock,<sup>8</sup> reviewing the literature in 1924, found only 3 instances of suppurative arthritis

Five cases of chronic meningococcic septicemia have been observed at the Lakeside Hospital during the last eleven years The unusual features of each will be discussed after its presentation

#### REPORT OF CASES

CASE 1—M H, a 25 year old woman, entered the medical service of the Lakeside Hospital on July 21, 1935, because of "rheumatism," red rash over the body and drowsiness progressing to coma She was known to be diabetic Ten days before admission a "sore throat" had developed, accompanied by pain and swelling of the wrists and knees Three days before admission a red rash had appeared over the body, especially on the chest, abdomen and back She became drowsy and eventually comatose There was no previous history suggestive of rheumatic fever

Physical examination showed a temperature of 40.2 C (104.4 F), a pulse rate of 140, a respiratory rate of 32 and a blood pressure of 122 systolic and 68 diastolic The patient was comatose Over the chest, abdomen and back and to a lesser extent over the extremities was a dull red, macular, purpuric eruption, each macule measuring about 2 mm in diameter None were confluent The tongue was red and swollen The breath had a strong odor of acetone The spleen was not palpable Both knees, both elbows and the left wrist were swollen, red, tender and painful on motion Over the dorsal aspect of the left wrist was a fluctuant mass, 5 cm in diameter Neurologic examination gave completely negative results

*Laboratory Findings*—The white cell count of the blood was 17,350, with a slight shift to the left, the red cell count, 3,260,000, with 70 per cent hemoglobin (Sahli) The sugar content was 444 mg per hundred cubic centimeters The carbon dioxide-combining power was 17.8 volumes per cent The urine showed acetone (4 plus) and diacetic acid, with 2.5 per cent sugar

*Course in the Hospital*—Vigorous treatment with insulin and parenteral fluids brought the diabetes under control High fever of the septicemic type continued, the temperature rising to 41.2 C (106.2 F) On the second day the subcutaneous abscess over the left wrist was incised, and several ounces of thick yellow pus was obtained Culture yielded organisms which fermented dextrose, lactose and maltose and were agglutinated by known antimeningococcus serum in a dilution of 1:640 Blood culture in brain broth yielded no definite growth, but a few gram-negative organisms were recovered, which failed to grow after transfer to a blood agar plate Subsequent blood cultures on brain broth, made on the third, the fourth, the fifth and the ninth day, were negative, although high fever continued At this time the left ear began to discharge a thin, brown pus The patient was given intravenously 10,000 units of meningococcus antitoxin (Parke-Davis) on the twelfth day and 20,000 units on each of the following



days through the sixteenth, a total of 90,000 units. This therapy had no effect, and the temperature frequently exceeded 40 C (104 F). Because of rapidly progressive anemia, the patient received several blood transfusions. On the thirty-fifth day a fluctuant area over the left scapula yielded 70 cc of yellow pus, from which organisms were cultured which agglutinated with antimeningococcus serum in a dilution of 1:2,560. On the fifty-seventh day a red, fluctuant, swollen area on the right thigh was aspirated and 10 cc of yellow pus obtained, which yielded only *Staphylococcus albus* on culture.

On the sixty-first day the left knee became swollen and fluctuant, seropurulent material obtained by aspiration yielded meningococci on culture, which were agglutinated by antimeningococcus serum (Lilly) in a dilution of 1:640. At the same time, roentgen examination of the second right metacarpal phalangeal joint revealed a destructive lesion. After the one hundred and eighth day the patient was afebrile. Strength and mobility of the left leg and right index finger returned. The abscesses over the left scapula, left wrist and right thigh healed readily after surgical incision. The patient was discharged on the two hundred and nineteenth day, at which time she could stand and take a few steps alone. The diabetes was well controlled.

*Follow-Up Report*—A year and nine months after discharge the patient was in good health. She walked normally and had only occasional stiffness in the left knee.

This is a case of chronic meningococcic septicemia lasting about four months. Although blood cultures were consistently negative, except in a single doubtful instance, the presence of septicemia cannot be questioned, because of the ease with which meningococci were recovered from the various widely disseminated abscesses. The unusual feature is the presence of suppurative arthritis of a knee joint and destructive (?) suppurative arthritis of a metacarpophalangeal joint. There were three large subcutaneous abscesses, from two of which meningococci were recovered. Treatment with the meningococcus antitoxin originated by Ferry<sup>17</sup> was without demonstrable effect. Antimeningococcus serum was not administered. Spontaneous recovery occurred after about four months of the disease.

CASE 2—I T, a 36 year old Russian Jewess, entered Lakeside Hospital on Dec 12, 1929, complaining of coldness and generalized pain, especially severe in the feet, of three months' duration. She stated that she had had similar attacks about once every three years for the twelve years preceding. Twelve years before she had been in another hospital for six weeks. Since then she had had three attacks characterized by fever, "spots" on the body, headache and malaise. All previous attacks had been preceded by a cold in the head with nasal discharge.

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<sup>17</sup> Ferry, N S, and Steele, A. Active Immunization with Meningococcus Toxin, *J A M A* **104** 983 (March 23) 1935. Ferry, N S. Meningococcus Antitoxin. I Prophylactic Therapeutic Tests on Guinea Pigs, *J Immunol* **23** 315, 1932, II Therapeutic Tests on Monkeys, *ibid* **23** 325, 1932, III Further Tests on Monkeys, *ibid* **26** 133, 1934, IV Further Tests on Guinea Pigs and Rabbits, *ibid* **26** 143, 1934. Hoyne, A L. Treatment of Meningococcic Meningitis Without Intraspinal Therapy, *Nebraska M J* **21** 321, 1936.

and cough. The present illness had begun three months before admission, with a feeling of chilliness, pain in the feet, shaking chills and sweats. She had lost 40 pounds (18.1 Kg.)

Physical examination showed marked enlargement of the liver, the spleen and right kidney were palpable. Over the body were multiple red papular lesions.

*Laboratory Findings*—The urine showed albumin and a few pus cells. The white cell count of the blood varied between 16,000 and 8,000, the red cell count was 3,800,000, with 65 per cent hemoglobin (Sahli). The Wassermann reaction was negative. Blood cultures taken on brain broth on the eleventh, the twenty-first and the thirtieth day in the hospital yielded meningococci which agglutinated with Parke-Davis antimeningococcus serum in a dilution of 1:1,600. The organism isolated from the blood stream was not agglutinated by the patient's own serum. The spinal fluid was normal.

*Course in the Hospital*—For the first eighteen days the patient had daily chills at the same hour each day, the temperature rising to 40°C with regularity. Chills and fever then became less regular. From the thirty-fourth to the thirty-ninth day she received 350 cc of antimeningococcus serum intravenously. After this time the fever was less marked, and after the sixtieth day the temperature was normal. Numerous blood cultures taken after the institution of serum therapy were negative, and the patient was discharged.

*Readmission*—She was readmitted nearly two years later, on Oct. 30, 1931. Since leaving the hospital she had continued to be weak and had become fatigued easily. A year before the second admission she had begun to cough and had vomited frequently and also had frequent epistaxes.

Physical examination again showed marked enlargement of the liver, now with prominent superficial veins on the abdomen. Moderate jaundice was present. The spleen was enlarged.

*Laboratory Findings*—The red cell count of the blood was 2,470,000, with 50 per cent hemoglobin (Sahli), the white cell count, from 13,400 to 9,800. The icterus index was 27. Blood culture on the fourteenth day in the hospital yielded meningococci.

*Course in the Hospital*—The temperature varied irregularly from 37.5 to 40.2°C (99.5 to 104.4°F). Bilateral bronchopneumonia developed on the fourteenth day in the hospital, and the patient died on the twenty-first day. She had received 100 cc of antimeningococcus serum intravenously two days before death.

*Autopsy*—The important pathologic diagnoses were cirrhosis of the liver, nephrosclerosis, bronchopneumonia and hemorrhage into the cerebellum. There is no record in the protocol of the autopsy of postmortem bacteriologic studies.

The patient had a history strongly suggestive of recurrent attacks of meningococcic septicemia over fourteen years, with six attacks during that time. The last two, two years apart, were observed in Lakeside Hospital, and the meningococcus was recovered from the blood stream on both occasions and from the nose and throat on the first occasion. It appears that the antimeningococcus serum given on the first admission was of value in shortening that attack, but there was recurrence two years later. On the last admission antiserum therapy was not instituted until the patient was moribund, and she died of causes probably unrelated to the meningococcic septicemia. There was no evidence of meningitis.

at any time, and the spinal fluid was consistently normal. The patient had regular daily chills and a "picket fence" type of fever on the first admission, but on the second admission the fever was irregular, and there were no chills.

**CASE 3**—A O, a 42 year old white man, was admitted to Lakeside Hospital on July 20, 1930, stating that six days before admission he had experienced marked malaise, with shaking chills and constant pain in the lower extremities. On the following day a diffuse red rash had appeared. He continued to be weak and drowsy, perspired and had pain in the legs.

Physical examination showed a diffuse maculopapular red rash involving the entire body except the scalp, soles and palms. A few of the lesions were pustular, and many were definitely purpuric.

*Laboratory Findings*—The red cell count of the blood was 4,400,000, with 66 per cent hemoglobin (Sahli), the white cell count, 20,000 to 10,000. Repeated blood cultures during the first four months yielded meningococci agglutinating with antimeningococcus serum (Lilly and Lederle), in dilutions of 1:640. The spinal fluid was normal.

*Course in the Hospital*—During the first five months fever was persistent, irregular and sometimes septic. At the end of this time the patient received a blood transfusion, after which the temperature gradually subsided. A spontaneous pneumothorax occurred on the left but subsequently disappeared. An autogenous meningococcus vaccine was prepared and was administered in small doses over a period of two weeks. During the last two of his six months' stay in the hospital the patient's improvement was gradual, with fewer recurrences of the purpuric rash. At the end of six months he was discharged symptom free and had not had a positive blood culture for two months.

*Readmission*—He was readmitted five years later, on March 1, 1935, complaining of frequent sharp, severe pain low in the back, associated with bouts of fever lasting two to three days. On three occasions he had observed a few scattered red lesions, the size of a pinhead, mostly on the legs but occasionally on the trunk. Physical examination showed no abnormality. Eight blood cultures yielded no growth. The temperature was normal, the patient was asymptomatic and was discharged without subjective or objective findings after ten days. No diagnosis was established. Unfortunately he was followed no further.

This is a typical case of chronic meningococcic septicemia lasting about four months. The patient was already improving when autogenous vaccine was given. Whether or not he experienced recurrent attacks during the five years between the first and second hospital admissions is impossible to say with certainty. Convalescence seemed to be accelerated after a blood transfusion.

**CASE 4**—J J S, a 19 year old white youth, was admitted to Lakeside Hospital on July 2, 1937, complaining of chills and fever of five weeks' duration. At the onset there was pain in the small toe of the right foot. No rash appeared on the skin at any time.

Physical examination showed no abnormality except a harsh systolic murmur at the apex of the heart. There was no antecedent history of rheumatic fever or heart disease.

*Laboratory Findings*—The red cell count of the blood was 4,570,000, with 74 per cent hemoglobin (Sahli), the white cell count was 17,400. Three blood cultures were positive for meningococci, but only after fourteen days' incubation.

*Course in the Hospital*—There were severe shaking chills daily, with elevation of temperature to over 40 C (104 F) each time for the first eighteen days. Severe anemia developed, and petechiae appeared in the palate and conjunctivas. Red blood cells were present in the urine. The systolic murmur became louder and rougher. The patient experienced pain in the left side of the chest, and this was followed by hemoptysis. He was given 140,000 units of Parke-Davis meningococcus antitoxin intravenously and large doses of sulfanilamide. A blood transfusion of 500 cc was given on the seventeenth day. After the eighteenth day there were no more chills, and the temperature became irregular, not exceeding 38.5 C (101.3 F). However, he became worse rapidly and died on the twenty-third day in the hospital. Permission for autopsy was refused.

This case is an instance of meningococcic septicemia progressing to a fatal termination in eight weeks. Clinically the patient exhibited signs of endocarditis, as evidenced by a rough, progressively louder systolic murmur, with petechiae and probably infarcts of the kidneys and left lung. No signs of meningeal irritation were present at any time. Meningococcus antitoxin and sulfanilamide had no effect, although they were not used until late in the course of the disease. It is interesting that after blood transfusion there were no further chills and the fever was considerably decreased, whereas before the transfusion severe chills and high fever occurred regularly twice a day. Although not proved by autopsy, a diagnosis of acute meningococcic endocarditis with multiple embolic phenomena seems justified.

CASE 5—T. A., a 32 year old white man, was admitted to Lakeside Hospital on Dec. 17, 1935, complaining of repeated chills for two weeks. Four months before admission he had begun to have migratory transient pains in the joints and muscles, with redness and swelling of many joints. At times his temperature had reached 38.3 C (100.9 F). Two weeks before admission he had had a shaking chill lasting fifteen minutes. Since that time he had had two or three shaking chills daily, associated with high fever.

Physical examination showed a pale, obviously ill man with cervical, axillary, epitrochlear and inguinal lymphadenopathy. The heart was normal. No murmurs were present. The spleen was palpable.

*Laboratory Findings*—The urine contained albumin and red cells. The red cell count of the blood was 2,500,000, with 72 per cent hemoglobin (Sahli), the white cell count, 12,000 to 19,000. Blood cultures on brain broth on the tenth, the twenty-first, the twenty-second, the twenty-third and the twenty-fifth day in the hospital yielded organisms subsequently proved to be meningococci and agglutinated by antimeningococcus serum (Lilly and Lederle) in dilutions of 1:1,280. The gonococcus complement fixation test was positive. Roentgen examination revealed bilateral polycystic kidneys.

*Course in the Hospital*—The patient had a severe shaking chill with elevation of temperature to 40 or 41 C (104 or 105.8 F) daily. He received a daily blood transfusion on the thirteenth, the fourteenth and the fifteenth day, because of progressive anemia. Because the organisms cultured from the blood were first

believed to be streptococci, he received 20 cc of antistreptococcus serum on the sixteenth and the eighteenth day. Later, because of the positive gonococcus fixation test, he received two injections of gonococcus filtrate intradermally. The identification of the organism was not completed until after the death of the patient, hence he was not treated with antimeningococcus serum. On the twentieth day a rough systolic and diastolic murmur appeared at the aortic area. These remained constant during the remainder of the course in the hospital. Petechiae were not observed at any time. On the twenty-seventh day the patient had a generalized convulsion and died. Permission for autopsy was not obtained.

While the diagnosis was not proved at autopsy, this was a case of chronic meningococcic septicemia apparently terminating with acute meningococcic endocarditis of the aortic valve. The temperature was of the "picket fence" type, with daily severe chills and high fever. Three blood transfusions, of 300, 400 and 500 cc, were without observable beneficial effect.

#### COMMENT

Because of the varied manifestations of infection with the meningococcus, it has been proposed<sup>18</sup> that the term "epidemic meningitis" should be abandoned and, further, that meningeal involvement should be considered as only one, albeit the most obvious manifestation of meningococcic infection. Herrick<sup>18</sup> suggested that meningococcic infection occurs in three stages: (1) acute infection of the upper part of the respiratory tract, (2) septicemia and (3) metastatic localization in various sites, including the meninges, joints, heart, lungs, pericardium and skin. Friedemann and Deicher<sup>19</sup> expressed the opinion that many catarrhal diseases of the respiratory tract are frequently due to unrecognized meningococcic infection.

In the cases here reviewed, 1 patient displayed purulent arthritis, and in addition numerous large subcutaneous abscesses. The presence of diabetes may have made this patient more susceptible to the formation of abscesses. Another of the patients had a history suggesting attacks of meningococcic septicemia over fourteen years, with two proved attacks two years apart. Two other patients gave good clinical evidence of acute endocarditis as a terminal event. These instances emphasize the variety of manifestations and the possible long duration of the disease.

The difficulty in culturing organisms is also demonstrated. Definitely positive blood cultures were never obtained in case 1, although the ease with which the organism was isolated from the numerous foci makes it obvious that septicemia did exist, at least intermittently. In case 4 blood

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18 Herrick, W. W. *Meningococcus Infections Including Cerebrospinal Fever*, in Christian, H. A., and Mackenzie, J. Oxford Medicine, New York, Oxford University Press, 1938, vol. 5, pt. 1, chap. 4, p. 77.

19 Friedemann, U., and Deicher, H. Ueber die Lenta-Form der Meningokokkensepsis, *Deutsche med. Wchnschr.* 52: 733, 1926.

cultures became positive only after fourteen days' incubation on enriched mediums. The necessity for prolonged incubation and the use of enriched mediums is further emphasized.

Effectiveness of specific treatment is not indisputable. It is generally agreed,<sup>20</sup> however, that the course of the disease is probably shortened by the use of specific antimeningococcus serum. One of the patients, although receiving adequate doses of meningococcus antitoxin, appeared to derive no benefit from the treatment. Carbonell and Campbell<sup>4b</sup> recently reported 3 cases of meningococcic septicemia and concluded that the most effective treatment is the use of the proper antimeningococcus serum in conjunction with sulfanilamide.

#### SUMMARY

Meningococcic septicemia, with its various metastatic lesions, is being recognized with increasing frequency.

There are an acute fulminating and a chronic type. The acute fulminating condition is invariably fatal. The chronic condition may last many months, and recovery is frequently spontaneous.

Five cases of the chronic type are reported. One patient had purulent arthritis, 1 had a history suggestive of attacks of the disease over fourteen years, and 2 presented clinical evidence of acute endocarditis.

Meningitis should be regarded as only one metastatic lesion of meningococcic septicemia. Lesions of the endocardium, myocardium, pericardium, lungs, sinuses, eyes, epididymis and joints also occur.

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20 Bloedorn, W. A. Meningococcus Septicemia, *Am J M Sc* **162** 881, 1921. Richter, A. B. Meningococcemia, *J A M A* **102** 2012 (June 16) 1934. Marlow, F. W. Meningococcemia, *ibid* **92** 619 (Feb 23) 1929. Clarke, F. B. Chronic Meningococcemia, *California & West Med* **34** 361, 1931. Le Bourdellès, B. De la fréquence de la meningococcie à forme purpurique, *Presse med* **33** 660, 1925. Appelbaum<sup>4a</sup>. Goundry and Phalen.<sup>9</sup>

# IS IRON EXCRETED BY THE GASTROINTESTINAL TRACT OF THE DOG?

A HISTOLOGIC STUDY

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The problem of the absorption and excretion of iron by the gastrointestinal tract remains baffling in spite of studies by numerous investigators during many years. The conclusions of many workers that iron is absorbed by the small and excreted by the large intestine have not been confirmed by recent investigations. Wallbach,<sup>1</sup> after repeating on mice the experiments of Hochhaus and Quincke, came to the conclusion that there is no morphologic criterion for the determination of whether iron is being absorbed or excreted, since the morphologic appearance of iron in the intestine is the same in the two instances. M'Gowan,<sup>2</sup> from a study of the literature and from observations on fowls suffering from hemolytic anemia, came to the conclusion that there is apparently "no justification for the statements current regarding the movements of iron in the body, namely that while absorption takes place solely from the duodenum, excretion is limited to the large intestine." A review of the literature on iron metabolism by Heath and Patek<sup>3</sup> indicated that excretion of iron by the bowel is probably extremely small, and the clinical observations of these authors confirmed

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1 Wallbach, G. Experimentelle Untersuchungen über die Verteilung und Ablagerung einiger medikamentöser Eisenpräparate, *Ztschr f d ges exper Med* 75 353, 1931

2 M'Gowan, J P. The Absorption and Excretion of Iron by the Intestines and the Nutritional and Therapeutic Value of Its Salts, *Edinburgh M J* 37 85, 1930

3 Heath, C W, and Patek, A J. The Anemia of Iron Deficiency, *Medicine* 16 267, 1937

the impression that, whereas gastrointestinal abnormality interfering with absorption of iron from the food may condition the development of anemia when there is rapid growth or excessive loss of blood, excretion of iron must play only a small part. Reimann, Fritsch and Schick,<sup>4</sup> Fowler and Barer<sup>5</sup> and Brock and Hunter<sup>6</sup> have recently found that when iron in large doses is given orally to patients with hypochromic anemia there is a much greater retention of iron than can be accounted for by the amount required for the formation of hemoglobin. This work has led to new speculations regarding the intrinsic metabolism of iron and has indicated the great capacity of the body to absorb and store iron and its relative inability to excrete iron. McCance and Widdowson<sup>7</sup> concluded that the power of the intestine to excrete iron has been greatly exaggerated. This conclusion has been confirmed by direct experimentation. Fowler and Barer<sup>8</sup> were unable to demonstrate an increased excretion of iron in the feces after the parenteral administration of iron to man. Henriques and Roland<sup>9</sup> observed that after the intravenous injection of iron citrate and iron lactate there was a small increase of iron in the urine but no increase in the feces. Henriques and Roche<sup>10</sup> also observed that there was no increase of iron in the isolated large bowel when iron lactate was given orally. Nicolaysen<sup>11</sup> recorded no increase of iron in the large or small bowel of the dog after the injection of iron. Numerous observations indicate that the bile contains only traces of iron even after the administration of iron orally and parenterally.

Clinically and experimentally, therefore, it appears that the excretion of iron by the gastrointestinal tract is an unimportant matter, and it may even be doubted that excretion in the ordinary sense takes place

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4 Reimann, F., Fritsch, F., and Schick, K. Eisenbilanzversuche bei Gesunden und bei Anämischen, *Ztschr f klin Med* **131** 1, 1936

5 Fowler, W. M., and Barer, A. P. Iron Retention Following Use of Ferric Ammonium Citrate in Hypochromic Anemia, *J. A. M. A.* **104**:144 (Jan 12) 1935

6 Brock, J. F., and Hunter, D. The Fate of Large Doses of Iron Administered by Mouth, *Quart J Med* **6** 5, 1937

7 McCance, R. A., and Widdowson, E. M. Absorption and Excretion of Iron, *Lancet* **2**:680, 1937

8 Fowler, W. M., and Barer, A. P. Retention and Utilization of Parenterally Administered Iron, *Arch Int Med* **60** 967 (Dec) 1937

9 Henriques, V., and Roland, H. Zur Frage des Eisenstoffwechsels, *Biochem Ztschr* **201**:479, 1928

10 Henriques, V., and Roche, A. Sur l'élimination intestinale du fer chez le chien, *Bull Soc chim biol* **12** 404, 1930

11 Nicolaysen, R. Untersuchungen über die Eisenausscheidung im Darmkanal bei Hunden. Beitrag zur Physiologie des Kolons, *Skandinav Arch f Physiol* **72**:126, 1935



at all from this organ. The following work was undertaken in order to determine whether by repeated histologic study of the intestines of dogs significant evidence for the excretion of iron could be demonstrated.

#### EXPERIMENTAL METHOD

A 4 cm section of the lower end of the colon was grafted with its blood supply intact to the abdominal wall by the colonic explant method of Drury, Florey and Florey<sup>12</sup>. This operation was performed on 4 dogs. The advantages of such a procedure are obvious. Repeated and frequent removal of material from the graft for histologic study is possible. The secretions of the graft can be collected and studied, at least qualitatively, for iron. The contents of the bowel are not in contact with the graft, so that the appearance of iron in histologic sections cannot be construed as indicating absorption of iron.

Iron was injected intramuscularly or intravenously daily or was given by mouth to these dogs and also to 2 normal dogs on which no operation had been done. Twenty to 100 mg of metallic iron was given daily by the parenteral route, iron and ammonium citrates in 10 per cent solution being employed. On a few occasions iron hydroxide in colloidal solution containing 1 mg of iron per cubic centimeter was employed for parenteral use. For oral use four to twelve tablets each containing 0.25 Gm of ferrous sulfate were given daily. Iron in these doses was well tolerated. No attempt was made to control the diet of the dogs, which consisted of bread, milk and meat.

Small pieces of the graft were removed at frequent intervals. No anesthetic was necessary, and the wounds healed well without the application of antiseptics. At less frequent intervals the dogs were anesthetized with ether, the abdominal cavity was opened under aseptic precautions and small pieces of tissue were removed from the following organs: the liver, the spleen, the fundus of the stomach, the duodenum (7 cm below the pancreatic duct), the lower portion of the ileum, the cecum and occasionally the colon. The wounds were sutured with silk, and the abdominal cavity was closed. After this operation a small piece of the graft and of the abdominal skin was removed. The tissues were placed in solution of formaldehyde U S P (redistilled in glass) and in Zenker's solution. Tissues fixed in formaldehyde solution were stained for iron by the potassium ferrocyanide method, careful precautions being taken against iron contamination. Tissues fixed in Zenker's solution were stained with hematoxylin and eosin. At first 50 per cent alcohol was employed as a fixative agent, but it had no particular advantages over solution of formaldehyde.

In dogs 1, 2, 3 and 4 a graft of the colon on the abdominal wall was performed. The transplantation of the graft took place about six months prior to the present experiments. Dogs 5 and 6 had no graft. From 2 additional dogs specimens of tissue from the liver and spleen were taken to be stained for iron.

#### PROTOCOLS

Dog 1 (German shepherd).—The animal weighed 15.6 Kg. Colloidal iron hydroxide was injected intravenously daily, the dose commencing with 20 cc and increasing gradually to 40 cc on the seventh day. The injections were continued until the forty-first day. Tissue for biopsy was taken from the graft before the injection of iron and on the fourth, sixth, eighth, sixteenth, thirty-fifth and one

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<sup>12</sup> Drury, A. N., Florey, H., and Florey, M. E. The Vascular Reactions of the Colonic Mucosa of the Dog to Fright, *J. Physiol.* 68: 173, 1929.

hundredth days Operation with removal of biopsy tissue from the internal abdominal organs and from the graft and skin was performed on the forty-first and one hundred and thirty-fifth days

Dog 2 (Hound) —The animal weighed 14.3 Kg Two cubic centimeters of solution of iron and ammonium citrates was injected intramuscularly daily for twenty-six days Three cubic centimeters daily was injected from the one hundred and sixty-eighth to the two hundred and third day Material for biopsy was taken from the graft twice before administration of iron and on the tenth, fifteenth, thirty-first and ninety-fourth days Operation with removal of biopsy tissue from the internal organs and from the graft and skin was performed on the twenty-sixth, one hundred and thirty-fifth and two hundred and third days

Dog 3 (Airedale) —The animal weighed 12.9 Kg Ferrous sulfate (1 Gm gradually increasing to 3 Gm daily) was given for forty days Intramuscular injection of iron and ammonium citrates was made daily in amounts of 2 to 3 cc from the one hundred and eighty-first to the two hundred and sixteenth day Tissue for biopsy was taken from the graft before administration of iron and on the third, fifth, seventh, sixteenth, thirty-sixth and one hundred and seventh days Operation with removal of biopsy tissue from the internal organs and from the graft and skin was performed on the forty-first, one hundred and forty-fourth and two hundred and sixteenth days

Dog 4 (Spaniel) —The animal weighed 12.7 Kg Ferrous sulfate (1 Gm gradually increasing to 3 Gm daily) was given for forty-one days Tissue for biopsy was removed from the graft before administration of iron and on the fourth, sixth, eighth, fourteenth and thirty-fourth days On the forty-second day the dog died under ether anesthesia, before operation Specimens from the internal organs and from the graft and skin were taken immediately

Dog 5 (Mongrel) —The animal weighed 25 Kg From 3 to 6 cc of a solution of iron and ammonium citrates was injected intramuscularly daily for fifty-three days Operation with removal of biopsy tissue from the internal organs and from the graft and skin was performed before the administration of iron and on the fifty-fourth day

Dog 6 (Mongrel) —The animal weighed 10 Kg From 3 to 6 cc of a solution of iron and ammonium citrates was injected intramuscularly daily for forty-four days Operation with removal of biopsy tissue from the internal organs and from the graft and skin was performed before the administration of iron and on the forty-fifth day

#### COMMENT

Qualitative tests for iron were performed repeatedly on the mucus collected from the grafts of the first 4 dogs but gave consistently negative results For these tests the following reagents were employed ammonium sulfide, sulfanilic acid and ammonium sulfocyanate

Microscopic examination of the sections of the graft which were first prepared with stock solution of formaldehyde as a fixative revealed appreciable amounts of iron deposited chiefly in the goblet cells of the mucosa but also throughout the connective tissue It was soon apparent that this iron was artefactitious It was present at times both before and after the administration of iron When solution of formaldehyde and water which had been redistilled in glass were employed, iron within

the mucous cells was always absent. The following experiments also were made. Sections were made and mounted from paraffin blocks of biopsy material from the graft, which did not show iron in the mucous cells. These sections were placed in 1 per cent ferrous sulfate for five minutes, washed in running water for about three minutes and stained for iron. All sections thus prepared contained large amounts of iron deposited particularly within the epithelial cells and in the connective tissue between and beneath the glands. It therefore appears that iron demonstrated within the epithelial cells and much of that in the connective tissue was an artefact and came from small amounts of iron in the solution of formaldehyde and in the washing fluids. Iron was present similarly within the epithelial cells when a dressing soaked in a solution containing 1 per cent ferrous chloride and 10 per cent dextrose was placed on the graft for twenty-four hours. No further trouble with this kind of artefact was experienced when extreme precautions were taken against contamination with iron. This experience nevertheless demonstrates a possible source of serious error in the interpretation of results based on the histologic study of iron in tissues.

Since the observations failed to demonstrate any definite evidence of iron in the process of excretion by the bowel, they will be reported only briefly. As may be anticipated, the liver and spleen of each animal contained large deposits of iron after the administration of this metal orally and parenterally. After the largest amounts of iron had been given for a prolonged period, hemosiderin granules were seen in the preparations of tissue from the liver and spleen fixed in Zenker's solution. The iron appeared intracellularly within phagocytes of the spleen and Kupffer cells of the liver but also throughout the pulp of the spleen in large masses and within the parenchymal cells of the liver. In contrast to the liver and spleen, the various parts of the gastrointestinal tract contained only traces of iron, the small intestine containing almost none and the stomach, large intestine, graft and skin showing traces which appeared to be increased after iron was administered. The iron found in these organs was always scattered in the connective tissue of the mucosa and submucosa and was never found within the mucous cells. In the skin, iron was deposited in the corium. Frequently these minute collections of iron appeared to be intracellular. They were sometimes in close approximation to small blood vessels.

Although the traces of iron found within the wall of the stomach and large intestine may be considered to be in the process of excretion, they may with at least equal probability be stored iron. In appearance the iron resembles that found in the skin, which is without much question stored iron or iron in a stage of transportation. In these observations the largest deposits of iron were in the liver and spleen.

This iron was certainly stored, even though eventually it may have shifted its position and character. Since traces of iron similar to those seen in the stomach and large bowel were seen in the graft, it is certain that they were not in the process of absorption. A section of the kidney of dog 4 after administration of iron revealed large traces of iron, chiefly intracellularly in the connective tissue between the tubules. It seems reasonable to believe that this, too, was stored iron.

#### CONCLUSION

Histologic study of the gastrointestinal tract and of a colonic explant on the abdominal wall of the dog before and after the administration of iron revealed no evidence that iron can be observed in the process of excretion by these organs. It seems reasonable to believe that the traces of iron seen in the walls of the stomach and the large bowel were in a state of storage rather than of excretion. Such a conclusion confirms the recently advanced opinion that the excretion of iron by the bowel is extremely small.

# Progress in Internal Medicine

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## BRIGHT'S DISEASE

### A REVIEW OF RECENT LITERATURE

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In this field the most conspicuous investigative activities during the past year have been concerned with renal factors in hypertension, growing out of Goldblatt's work. Interest has been sustained in the nature of glomerulonephritis, in the renal disorders of pregnancy and in pyelonephritis. Studies of renal function have been concerned with intermediate steps in the formation of urine in health and in disease.

### GLOMERULONEPHRITIS

Baehr<sup>1</sup> takes issue with those who would make a diagnosis of diffuse glomerulonephritis on the basis of urinary abnormalities alone or on the postmortem observation of diffuse glomerular changes in diseases, such as rheumatic fever, in which manifestations of nephritis are inconspicuous or lacking. Since glomerulonephritis must be considered a general vascular disease, of which the renal lesions are only a part, there should be evidence of extra-renal vascular damage to substantiate a diagnosis. He points out the rarity of gross clinical manifestations of glomerulonephritis in rheumatic fever as an argument that the diffuse glomerular changes previously described by Bell are not to be taken as evidence of true nephritis.

The opposite point of view is presented by Murphy and Rastetter,<sup>2</sup> who show that a considerable number of patients present themselves with chronic glomerulonephritis who have no knowledge of an acute phase of the disease. Furthermore, mild, subclinical forms of the disease are frequently observed, which present at first only urinary abnormalities, yet nevertheless progress to outspoken chronic glomerulonephritis. These facts are cited in support of Bell's view that innumerable transitions occur between subclinical and clinical glomerulonephritis. These are of great importance in establishing the links of evidence.

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1 Baehr, G. The Nature of Glomerulonephritis, *Bull New York Acad Med* 14 53 (Feb) 1938.

2 Murphy, F D, and Rastetter, J W. Acute Glomerulonephritis, with Special Reference to the Course and Prognosis. A Study of One Hundred and Fifty Cases, *J A M A* 111 668 (Aug 20) 1938.

between chronic glomerulonephritis and the less obvious etiologic factors in this disease

Murphy and Rastetter<sup>2</sup> consider acute glomerulonephritis to exist if hematuria, albuminuria and cylindruria persist for a week, even if extrarenal vascular phenomena are lacking. Loeb<sup>3</sup> requires the persistence of these signs for ten to fourteen days and thinks it best to admit doubt if extrarenal vascular phenomena are lacking. He concludes that the percentage of cases of recovery and the proportion of cases in which the condition becomes chronic, as reported by different authors, vary because of the differences in criteria on which a diagnosis of acute nephritis is based.

Murphy and Rastetter<sup>2</sup> record the outcome of acute glomerulonephritis in 150 cases. Of the 150 patients, 105 were under 30 years of age. Of the latter, 50 per cent recovered, 40 per cent became chronically ill and 10 per cent died. Of the patients over 30 years of age, about 50 per cent recovered, 25 per cent became chronically ill and 25 per cent died. They remark that the disease may run its whole course without hypertension. Elevation of blood pressure was noted in only one third of the cases in which recovery occurred, in one half of the cases in which the disorder became chronic and in one third of the fatal cases.

The observations of Murphy and Rastetter have led them to the conclusion that persons in whom chronic nephritis develops, even years after an acute attack, have had continuous inflammation of the kidneys (prolonged latency) or chronic activity punctuated by remissions and exacerbations induced by attacks of infection of the upper respiratory tract. Baehr<sup>1</sup> also believes that patients who have had acute glomerulonephritis have suffered severe and permanent damage to the kidneys. Even though recovery seems to be complete for years, pregnancy or intercurrent infection may precipitate a recurrence. In cases of supposed recovery, arterial hypertension may develop insidiously.

Regarding the question of permanence of recovery in acute glomerulonephritis, Loeb, Lyttle, Seegal and Jost<sup>4</sup> report that in 8 of 10 cases in which the disorder was preceded by hemolytic streptococcal infection, healing occurred in from eight months to three years. Thereafter in each instance no recurrence of the nephritis was noted when intermittent hemolytic streptococcal infection occurred. In the 2 remaining cases transient urinary abnormalities were noted with intercurrent infection, however, in none of the 10 cases did the condition become chronic. Loeb<sup>3</sup> states that once the urinary picture has returned completely to

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3 Loeb, R. F. Clinical Aspects of Nephritis, *Bull. New York Acad. Med.* **14** 65 (Feb.) 1938.

4 Loeb, E. N., Lyttle, J. D., Seegal, D., and Jost, E. L. On the Permanence of Recovery in Acute Glomerulonephritis, *J. Clin. Investigation* **17** 623 (Sept.) 1938.

normal, there is little danger of the development of chronic nephritis. He has observed many patients with this type of condition who have had recurrent infection of the upper respiratory tract which has not resulted in the reappearance of urinary abnormalities.

The importance of the erythrocyte sedimentation rate as an index of activity in glomerulonephritis is mentioned by Murphy and Rastetter,<sup>2</sup> who report that it is high in the acute stages and that it diminishes as healing occurs. The titer of antistreptolysins in the serum is shown by Lyttle, Seegal, Loeb and Jost<sup>5</sup> to be related to the severity, persistence and recurrence of hemolytic streptococcic infections. However, these observers were unable to find any significant correlation between the antistreptolysin titer and the severity or duration of acute nephritis or the tendency for chronic nephritis to develop.

Baehr<sup>1</sup> mentions the frequency of acute myocarditis in acute nephritis. Rubin and Rapoport<sup>6</sup> report 14 instances of acute myocardial involvement in 55 cases of acute nephritis, evidence of which was found in dyspnea, tachypnea, cough, enlargement of the heart, muffled heart tones, rapid rate, murmurs, gallop sounds, signs of congestive failure and abnormalities of the electrocardiogram. In all 55 cases the only deaths which occurred were from heart failure, which appeared to be precipitated by hypertension. In the treatment of these patients they recommend restriction of fluids and the use of a 50 per cent solution of magnesium sulfate, in doses of 0.2 cc per kilogram of body weight, by intramuscular injection.

Langendorf and Pick<sup>7</sup> discuss the electrocardiogram in acute nephritis. The changes most frequently found were (a) flattening of the T wave in lead I or a peculiar bifid T wave in some cases, (b) discordant changes in the final deflections in lead III, the T wave becoming a large upright summit, and (c) reversal of direction of the normally negative T wave in lead IV, with an occasional bifid T<sub>4</sub>. These changes differ from those accompanying occlusive lesions in the anterior wall of the left ventricle in that ST deviations do not occur, Q<sub>1</sub> does not develop and Q<sub>4</sub> does not disappear. Bifid T waves are not observed in cases of arterial occlusion.

Ehrstrom<sup>8</sup> reviews the evidence which connects glomerulonephritis, periarteritis and rheumatic arteritis with allergy, taking the view that

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5 Lyttle, J. D., Seegal, D., Loeb, E. N., and Jost, E. L. The Serum Anti-streptolysin Titre in Acute Glomerulonephritis, *J Clin Investigation* **17** 631 (Sept) 1938.

6 Rubin, M. I., and Rapoport, M. Cardiac Complications of Acute Hemorrhagic Nephritis, *Am J Dis Child* **55** 244 (Feb) 1938.

7 Langendorf, R., and Pick, A. Elektrokardiogramm bei akuter Nephritis, *Acta med Scandinav* **94** 1 and 36, 1938.

8 Ehrstrom, M. C. Irreversible, Allergic Reactions with Non-Bacterial Antigen, *Acta med Scandinav* **94** 346, 1938.

they are all irreversible reactions of an allergic nature, due in some cases to bacterial antigens and in other instances to food antigens. He describes a case in which signs of acute diffuse glomerulonephritis, manifested by hematuria, albuminuria, cylindruria and edema, developed with the eating of certain fruits by a patient with food allergy. The symptoms would disappear if the foods were withdrawn, and exacerbations could be induced by testing with food antigens.

The experimental glomerulonephritis produced by the use of nephrotoxic serum (Masugi-Smadel) has been studied by Ehrich, Wolf and Bartol.<sup>9</sup> These observers show that the structural and functional changes in this form of experimental nephritis in rabbits are the same as those of glomerulonephritis in human beings. In its pathogenesis the disease begins with a period of latency characterized by hyperemia of the glomeruli and in a number of cases by increased diuresis. In view of this finding the angiospastic theory of Volhard is untenable. Proliferation of glomerular cells is the typical lesion of the acute phase. Oliguria, marked proteinuria and diminished glomerular filtration (measured with cyanol) occur at the time when the glomerular changes are at their peak and are chiefly attributable to glomerular injury. In the acute phase excretion of azofuchsin I was not diminished except in 1 rabbit which at autopsy showed fatty changes in the tubules. Elsewhere these authors have shown that azofuchsin I is eliminated largely by tubular activity. Hence they conclude that in initial acute nephritis, the glomeruli and tubules may function independently of each other.

Hamori and Koranyi<sup>10</sup> have studied the influence of denervation of the kidneys on experimental glomerulonephritis (Masugi). They found that denervation of the kidneys of animals subjected to injections of nephrotoxin did nothing except prevent prealbuminuric retention of water. The subsequent development of Masugi nephritis and hypertension proceeded in the same way as in animals not subjected to denervation.

#### NEPHROSIS

Murphy, Warfield, Grill and Annis<sup>11</sup> discuss the controversial point as to whether true lipid nephrosis exists as an entity distinct from glomerulonephritis. They report 9 cases which they regard as instances of genuine lipid nephrosis. Two of the patients died, and careful histo-

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9 Ehrich, W. E., Wolf, R. E., and Bartol, G. M. Acute Experimental Glomerular Nephritis in Rabbits. A Correlation of Morphological and Functional Changes, *J. Exper. Med.* **67** 769 (May) 1938.

10 Hamori, A., and Koranyi, A. Der Einfluss der Entnervung der Nieren auf die Masugi-Nephritis, *Ztschr. f. klin. Med.* **133** 722, 1938.

11 Murphy, F. D., Warfield, L. M., Grill, J., and Annis, E. R. Lipoid Nephrosis. A Study of Nine Patients with Special Reference to Those Observed Over a Long Period, *Arch. Int. Med.* **62** 355 (Sept.) 1938.



logic study of the kidneys at autopsy revealed no evidence of glomerular lesions. Six patients recovered, and 1 still remains under observation. They conclude that pure lipid nephrosis is a rare disease but that it is an entity distinct from glomerulonephritis. They believe there is good reason to retain the distinction.

In a study of the intraocular pressure of an edematous patient with the nephrotic syndrome, Robertson<sup>12</sup> found no relation between the colloid osmotic pressure of the plasma and the intraocular pressure, which remained constant and normal through all variations in colloid osmotic pressure. The inference drawn from these observations is that the aqueous humor is not a simple dialysate.

#### PYELONEPHRITIS

In previous reviews considerable attention has been given to the renewed interest in chronic pyelonephritis as an insidious disease frequently associated with hypertension and ultimately with failure of renal function. Fahr<sup>13</sup> has recently reviewed the pathologic changes of ascending pyelonephritis, which, he states, is the commonest inflammatory disease of the kidney. Contracted kidneys, which have a struma-like appearance owing to dilatation of tubules and cysts, sometimes show what he regards as evidence of hypogenesis of the renal calices. This developmental defect is regarded by Fahr as a predisposing cause of the ascending infection.

Schaffer and Remsen<sup>14</sup> discuss the relation of urinary infection to chronic nephritis of childhood. Twenty cases in which the diagnosis of chronic interstitial nephritis was made were reviewed. Of these, 15 were undoubted examples of chronic pyelonephritis, yet "pyelitis" had been recognized *intra vitam* in only 5. Only 1 of the 15 patients was a male. The characteristic features do not lie in the history of the illness, they are to be found in the demonstration of a disproportionate pyuria, of coliform infection of the urine and of anatomic lesions of the genito-urinary tract. They believe that the infection is ascending rather than hematogenous. They discuss the possibility that ureteral strictures occur as a result of acute cystitis and that subsequently this results in damage to the upper urinary passages and kidney. Three different types of the malady were observed: (a) a type seen in the majority of cases, hypertension and renal insufficiency developing with equal rapidity, (b) a type associated with renal rickets but no hypertension as seen in a few chil-

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12 Robertson, J. D. Intraocular Pressure in Nephrotic Oedema and Its Bearing on the Nature of the Aqueous Humor, *Lancet* **1** 1435 (June 25) 1938.

13 Fahr, T. Ueber pyelonephritische Schrumpfnieren und hypogenetische Nephritis, *Virchows Arch f path Anat* **301** 140, 1938.

14 Schaffer, A. J., and Remsen, D. The Relation of Urinary Infection to Chronic Nephritis in Childhood, *Acta pædiat* **22** 415, 1938.

dien, and (c) a type characterized by an inordinate degree of hypertension. They conclude that chronic pyuria must be regarded as a serious symptom and that treatment, with the aid of a urologist, must be given early in the course of the disease if disastrous late results are to be avoided. The persistence of pyelonephritis for several months may make fatal renal insufficiency inevitable.

#### RENAL DISEASE AND PREGNANCY

Peters<sup>15</sup> reviews the evidence of the importance of pyelitis in the "toxemias of pregnancy." Of 203 patients observed, 49 died of renal or vascular disease, 67 had residual renal or vascular disease and 69 had subsequent attacks of "toxemia," leaving only 15 alive without residual incapacity a year or more after the most recent attack of "toxemia." Among the so-called toxemias are to be found conditions resembling all the disorders which outside of pregnancy give rise to arteriolar disease, hypertension or functional impairment of the kidney. Peters can find no evidence of abnormal metabolism or derangement of the endocrine glands in the causation of these disorders. He regards it as probable that the ureteral obstruction of pregnancy predisposes to an unusually severe reaction of the kidney or vascular system to insults which might in the nonpregnant state produce less severe disturbance. It may be that decrease of protein, bicarbonate and sodium and increase of lipoids in the plasma are factors in the heightened susceptibility of the pregnant woman to these disorders. These observations of Peters reveal the fact that "toxemias" of all kinds leave behind them marks which cannot be eradicated. He believes that this warrants the prevention of pregnancy in the woman who has disease of the arteries or kidneys or who has had "toxemia" and the immediate termination of pregnancy on the first sign of hypertension and renal disease.

Regarding the question of the permissibility of further pregnancies after "late toxemia," Wood and Nix<sup>16</sup> state that definite derangement of renal function is the most important contraindication to further pregnancy. If renal function is found to be normal, the advisability of permitting further pregnancy may be determined by repeated observation of the blood pressure and retinas and a consideration of the age factor (older women show a greater tendency to toxemia). These authors recall in this connection that Elden, Sinclair and Rogers found that two thirds of the women with eclampsia whom they studied had low values for urea clearance three months after delivery. Also they

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15 Peters, J. P. The Nature of the Toxemias of Pregnancy, *J. A. M. A.* **110** 329 (Jan. 29) 1938.

16 Wood, J. E., and Nix, H. Hypertension in the Late Toxemias of Pregnancy, *J. A. M. A.* **110** 332 (Jan. 29) 1938.

call attention to the observations by Stander and Peckham, who found that the mortality among pregnant women who had chronic nephritis was 42.5 per cent within ten years, a rate which is five and one-half times the average mortality rate for women in the same age group.

Supporting the ideas expressed by Peters on the nature of so-called toxemias, Page<sup>17</sup> reports that he was unable to demonstrate the presence in the blood of women with eclampsia any pressor substance or toxin or evidence of hypersecretory activity of the pituitary in experiments in which the blood of eclamptic women was transfused into normal pregnant women. As control experiments, normal blood was also given to such women, and observations were made on the blood pressure and urinary output. When the normal donor was given large amounts of solution of posterior pituitary before withdrawal of blood, no anti-diuretic response was noted in the recipient.

The retention of water in the last trimester of pregnancy was found by Strauss<sup>18</sup> to amount to as much as 10 per cent of the body weight, whether edema was visible or not. This retention of water is believed to be conditioned by the low protein content of the plasma. If the intake of sodium is kept constant, retention of water is inversely proportional to the osmotic pressure of the plasma protein. Unless the plasma protein is below a certain critical level, a diet consisting of 1,500 cc of skimmed milk daily will result in the elimination of the retained water. This diet is low in sodium (0.6 Gm) and relatively high in calcium and potassium. Patients on this diet were tested for periods of five days, and the amount of weight was plotted against the colloid osmotic pressure. Patients whose venous pressure was more than 15 cm of water were excluded from the tests. Strauss concludes that the retention of water in pregnant women does not differ from that in nonpregnant women.

Various writers propose somewhat different procedures for the management of the toxemias of pregnancy. Dodge and Frost,<sup>19</sup> in view of the low concentration of albumin frequently found in the plasma, recommend giving 80 Gm of protein daily in the diet. In the discussion of their paper, Thomas Addis pointed out that his observation of pregnant rats showed that it was difficult for the mother rat to ingest sufficient

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17 Page, E. W. The Effect of Eclamptic Blood upon the Urinary Output and Blood Pressure of Human Recipients, *J. Clin. Investigation* **17** 207 (May) 1938.

18 Strauss, M. B. Observations on the Etiology of the Toxemias of Pregnancy. IV. The Primary Role of the Plasma Proteins in Conditioning Water Retention and Edema Formation in Normal and Toxemic Pregnancy, *Am. J. M. Sc.* **195** 723 (June) 1938.

19 Dodge, E. F., and Frost, T. T. Relation Between Blood Plasma Proteins and Toxemias of Pregnancy, *J. A. M. A.* **111** 1898 (Nov. 19) 1938.

protein to maintain the plasma protein in normal amount in the presence of the great demand for protein made by the growing fetus Davis <sup>20</sup> on the other hand, recommends a low protein diet poor in salt and depends on intravenous injections of hypertonic solutions of dextrose to secure diuresis McPhail <sup>21</sup> recommends ingestion of large quantities of fluid and a diet low in protein

If convulsions occur Davis <sup>20</sup> recommends the use of morphine,  $\frac{1}{4}$  grain (0.016 Gm) every hour, until the convulsions cease or the respiratory rate drops to 12 After each convulsion an injection is given intramuscularly of 10 cc of a 25 per cent solution of magnesium sulfate Nothing is given to the patient by mouth until after she is conscious, when 50 cc of 10 per cent Karo syrup is given by stomach tube, this is repeated every hour in amounts increasing by 50 cc each time until 200 cc is given

#### RENAL HYPERTENSION

The use of the Goldblatt clamp for the production of hypertension through partial ischemia of the kidney is now familiar in many laboratories A variation of this process has been used by Drury,<sup>22</sup> who puts a loop of silk thread around one renal artery of a young rabbit As the animal grows, the vessel is gradually constricted, and hypertension results without renal insufficiency, since the other kidney is intact When the normal kidney is removed the hypertension is increased Friedman and Katz <sup>23</sup> injected trypsin into both renal arteries and in this way produced chronic renal insufficiency without hypertension When Goldblatt clamps were applied, the blood pressure rose If the clamp was applied to one side only, hypertension was noted, but the blood pressure fell again if the ischemic kidney was removed It is clear, therefore, that renal hypertension is quite independent of renal insufficiency and not dependent on retention of toxic substances

In 1924 Major and Stephenson tried to associate the guanidine bases with clinical hypertension Child <sup>24</sup> has reinvestigated this question He finds that guanidine bases increase in the blood in a manner roughly

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20 Davis, M. E. Water Balance in Relation to the Toxemias of Pregnancy, Surg, Gynec & Obst **66** 426 (Feb) 1938

21 McPhail, F. L. Treatment of Toxemias of Pregnancy, J. A. M. A **111** 1894 (Nov 19) 1938

22 Drury, D. R. The Production by a New Method of Renal Insufficiency and Hypertension in the Rabbit, J. Exper. Med **68** 693 (Nov) 1938

23 Friedman, M., and Katz, L. N. Renal Insufficiency Following Trypsin Injection into the Renal Arteries, J. Exper. Med **68** 485 (Oct) 1938

24 Child, C. G. The Guanidine Bases in the Blood of Dogs with Experimental Hypertension Produced by Constriction of the Renal Arteries, J. Clin. Investigation **17** 301 (May) 1938

proportional to the increase in nonprotein nitrogen following procedures which produce renal insufficiency. After unilateral ligation of a renal artery the amount of guanidine bases sometimes rose, but only if the non-protein nitrogen content also rose. No etiologic relation could be established between the experimental hypertension from constriction of the renal arteries and the appearance of guanidine bases in the blood stream. In some animals with hypertension of six to eight months' duration, the values for both blood urea and guanidine bases were within normal limits, though the blood pressure was far above normal.

Comparison of the effects of pressor drugs and the pressor substance found in saline extracts of kidneys has been made by Landis, Montgomery and Sparkman<sup>25</sup>. Saline kidney extracts were heated to 55 to 56 C and saturated with ammonium sulfate, thus yielding a precipitate which after solution and dialysis produced a conspicuous rise in blood pressure without diminution of the temperature of the skin or of the amplitude of arterial pulsations. Thus the pressor substance produced in the kidney differs from epinephrine, tyramine, guanidine and its derivatives, solution of posterior pituitary, pitressin, ergotoxine and ergotamine, all of which cause a decrease in the temperature of the skin and a diminution in the blood flow in the ear of the heated rabbit.

A study of the renal arteries in relation to age and arterial hypertension has been made by R. H. Williams and T. R. Harrison<sup>26</sup>. Three groups of patients were investigated post mortem: (a) elderly persons with benign hypertension, in whom the predominant change was narrowing of the large renal arteries, (b) middle-aged persons with malignant hypertension, in whom the predominant change was narrowing of the afferent arterioles to the glomeruli, and (c) young hypertensive patients with glomerulonephritis, who showed narrowing of the renal arterioles. Rosenberg, Keith and Wagener<sup>27</sup> found lesions of the renal arteries associated with mild or fluctuating hypertension, while in patients with sustained hypertension they found lesions of the arterioles. Leiter<sup>28</sup> reports a case of hypertension coming on acutely in a man who had extensive bilateral thromboarteritis of the small renal arteries.

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25 Landis, E. M., Montgomery, H., and Sparkman, D. The Effects of Pressor Drugs and of Saline Kidney Extracts in Blood Pressure and Skin Temperature, *J. Clin. Investigation* **17** 189 (March) 1938.

26 Williams, R. H., and Harrison, T. R. A Study of the Renal Arteries in Relation to Age and to Hypertension, *Am. Heart J.* **14** 645 (Dec.) 1937.

27 Rosenberg, E. F., Keith, N. M., and Wagener, H. P. Diffuse Arterial Disease with Hypertension. Two Unusual Cases of Contrasting Types, *Arch. Int. Med.* **62** 461 (Sept.) 1938.

28 Leiter, L. Unusual Hypertensive Disease, *J. A. M. A.* **111** 507 (Aug. 6) 1938.

Freeman and Hartley<sup>29</sup> record the case of a patient who had unilateral nephrectomy for traumatic rupture of the kidney. Subsequently hypertension developed, and at autopsy the orifice of the large artery of the remaining kidney was greatly narrowed by an atheromatous plaque. The foregoing observations show the conditions of the arteries which are associated with partial ischemia of the kidneys and hypertension.

Rytand<sup>30</sup> demonstrated that the elevation of blood pressure which is observed in persons with coarctation of the aorta is due to the action of the pressor substance formed in the ischemic kidneys. In experiments on animals, if the aorta was constricted proximal to both renal arteries, hypertension resulted if there was living renal tissue. No elevation of blood pressure occurred if nephrectomy had been done, although the mechanical effects of aortic constriction were the same.

Grossman and Williams<sup>31</sup> gave extracts containing renal pressor substance to rats of various ages. The doses administered were proportional to the body surfaces of the animals. The youngest rats showed the least and the oldest the greatest pressor response. When the kidneys of young and old rats were assayed for pressor substance, the greater amounts were found in those of young rats and the lesser in those of old rats. They comment on these experiments in relation to the fact that a larger proportion of elderly than of young persons exhibit hypertension.

High blood pressure is sometimes found in association with hydronephrosis. This phenomenon was investigated by Williams, Wegria and Harrison,<sup>32</sup> who observed well marked hypertension in rats with spontaneous bilateral hydronephrosis. Such rats gave a greater pressor response when they received injections of renal pressor substance. Furthermore, extracts prepared from hydronephrotic kidneys gave greater pressor effects than those derived from normal kidneys. The same results were obtained when the hydronephrosis was produced by ligation of the ureters.

#### STUDIES OF RENAL FUNCTION

Chesley<sup>33</sup> has studied urea clearance during oliguria. When the volume of urine falls below 0.35 cc per minute, the urea concentration

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29 Freeman, G., and Hartley, G. Hypertension in a Patient with a Solitary Ischemic Kidney, *J A M A* **111** 1159 (Sept 24) 1938.

30 Rytand, D. A. The Renal Factor in Arterial Hypertension with Coarctation of the Aorta, *J Clin Investigation* **17** 391 (July) 1938.

31 Grossman, E. B., and Williams, J. R., Jr. Relation of Age to Renal Pressor Substance, *Arch Int Med* **62** 799 (Nov) 1938.

32 Williams, J. R., Jr., Wegria, R., and Harrison, T. R. Relation of Renal Pressor Substance to Hypertension of Hydronephrotic Rats, *Arch Int Med* **62** 805 (Nov) 1938.

33 Chesley, L. C. Urea Excretion at Low Urine Volumes. The Calculation of "Minimal" Urea Clearances, *J Clin Investigation* **17** 119 (March) 1938.

ratio becomes fixed so that further decrease in volume does not affect the ratio of urine urea to blood urea. A formula is suggested by means of which these minimal clearances can be related to those obtained under standard or maximal conditions. In a subsequent paper Chesley<sup>34</sup> reports that with low urinary volumes, urea and creatinine become maximally concentrated in the urine. The plasma clearance values for endogenous creatinine have a linear arrangement in the range of urinary volumes of 0.35 to 0.5 cc per minute, this suggests that these urinary volumes vary directly with the rate of glomerular filtration and implies a constant and maximal resorption of water.

Attempts are now being made to study separately and quantitatively tubular and glomerular function. Smith, Goldring and Chasis<sup>35</sup> find that phenolsulfonphthalein, diodrast and hippuran are excreted by a common cellular mechanism in the tubules. This tubular action has a maximal limiting value, hence these authors take maximal clearances of these three substances as a measure of the tubular mass. Glomerular filtration is measured by the inulin clearance. From data on these observations the authors calculate the renal blood flow at about 1,300 cc per minute and the glomerular filtration at 137 cc per minute for a man with a surface area of 1.73 square meters under basal conditions.

Chasis and Smith<sup>36</sup> studied the simultaneous excretion of urea and inulin. In the case of inulin the ratio of values for the urine and the plasma is a measure of the degree of concentration of the glomerular filtrate. The urea clearance was less than the volume of the filtrate in both normal and nephritic subjects, showing that urea is invariably resorbed to some extent. It was found that as the capacity of the tubule to resorb water is impaired by disease, the fraction of urea resorbed decreases, so that the value of the urea clearance approaches that for glomerular filtration. There was no evidence in any case to indicate an increased back diffusion of urea.

A somewhat contrary view is presented by Nicholson, Urquhart and Selby<sup>37</sup>. These investigators produced injury to one kidney by perfusing it with sodium tartrate, leaving the other intact. The nephrosis produced was limited to the proximal convoluted tubule, with no histologic evi-

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34 Chesley, L. C. Renal Excretion at Low Urine Volumes and the Mechanism of Oliguria, *J Clin Investigation* **17** 591 (Sept) 1938

35 Smith, H. W., Goldring, W., and Chasis, H. The Measurement of the Tubular Excretory Mass, Effective Blood Flow and Filtration Rate in the Normal Human Kidney, *J Clin Investigation* **17** 263 (May) 1938

36 Chasis, H., and Smith, H. W. The Excretion of Urea in Normal Man and in Subjects with Glomerulonephritis, *J Clin Investigation* **17** 347 (May) 1938

37 Nicholson, T. F., Urquhart, R. W. I., and Selby, D. L. Renal Function as Affected by Experimental Unilateral Kidney Lesions. Nephrosis Due to Sodium Tartrate, *J Exper Med* **68** 439 (Sept) 1938

dence of glomerular damage After perfusion of the kidney the bladder was opened, and separate functional studies were made of each kidney The excretion of water and of chloride was disturbed in the injured kidney, and the clearances of urea, xylose, inulin, creatinine and phenol-sulfonphthalein were diminished The clearance of ferrocyanide was diminished, this substance was found in the damaged tubular cells of the injured kidney but not in the normal one Hence the authors hold that increased back diffusion may render inulin and creatinine unsuitable for the measurement of glomerular filtration in conditions in which the tubules are damaged

Chasis, Ranges, Goldring and Smith<sup>38</sup> made observations on water diuresis and the action of oil of juniper, epinephrine, theophylline, caffeine, sodium nitrate and artificial fever, in which the total renal blood flow and the glomerular filtration were estimated Their experiments led to the conclusion that the blood flow of the kidney is regulated by the efferent renal artery Since an increase or decrease in blood flow is accompanied by inverse changes in the filtration fraction, the rate of filtration tends to be independent of the normal variations in renal blood flow It is believed that the vasomotor control of the efferent artery is independent of the mechanism by means of which the blood pressure is regulated through the carotid sinus

#### RENAL INSUFFICIENCY FOLLOWING BLOOD TRANSFUSION

DeGowin, Warner and Randall<sup>39</sup> have thrown new light on the mechanism of renal insufficiency occurring in incompatible blood transfusions Transfusion of canine hemoglobin into dogs when the urine is acid results in death from renal insufficiency This does not occur when the urine is alkaline The anatomic picture was that of obstruction of the tubules by pigment when the urine was acid In 9 patients who died of renal insufficiency following hemolysis, two processes were observed (1) the obstruction of tubules with pigment and (2) a degeneration of tubular epithelium and interstitial edema The obstruction of tubules might be prevented if the urine was alkalinized prior to the transfusion, but the authors doubt whether the nephrotoxic process would be limited by that procedure

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38 Chasis, H , Ranges, H A , Goldring, W , and Smith, H W The Control of Renal Blood Flow and Glomerular Filtration in Normal Man, *J Clin Investigation* **17** 683 (Sept ) 1938

39 DeGowin, E L , Warner, E D , and Randall, W L Renal Insufficiency from Blood Transfusions II Anatomic Changes in Man Compared with Those in Dogs with Experimental Hemoglobinuria, *Arch Int Med* **61** 609 (April) 1938



## Correspondence

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### ELECTIVE LOCALIZATION AND INFECTIONS OF THE RESPIRATORY TRACT

*To the Editors* —Polemics should have no place in science. I have consistently refrained from them and shall continue to refuse to try to convince by argument alone those whose views are at variance with my own. Differences founded on experiment I have considered from time to time as occasion demanded by the presentation of new or additional data and, incidental to these, have indicated so far as possible wherein lay the reason for the discrepancies.

The statements by Reimann with regard to my work on elective localization and on the use of vaccines in cases of infections of the respiratory tract are so misleading as to require consideration<sup>1</sup>. I can point out only (1) that from his list of diseases in which I have presented evidence indicating streptococci as the etiologic factors, he omitted four—ulcer of the stomach and duodenum, cholecystitis and gallstones, canine encephalomyelitis and equine encephalomyelitis—and that he neglected to state that my results have been corroborated by my associates and independently by others for most of the diseases he listed, (2) that he neglected to mention the fact that Schottmuller was the only person who really voiced disagreement with my views on elective localization at the German Congress of Internal Medicine at Wiesbaden, (3) that Schottmuller admitted in the open discussion on that occasion that the principle of elective localization was applicable in some cases, (4) that the discussion or rather presentation of confirmatory studies by many, some of whom voiced emphatic disagreement with Schottmuller's views, exceeded fourfold the allotted time for my paper, and (5) that in making rounds with Schottmuller several weeks later, an invitation I accepted at the time of the congress, I found much evidence of focal infection in his patients which had been entirely overlooked by him. Infection was actually demonstrated in 5 patients during my short visit. One had recurring attacks of cholecystitis, 2 had suffered from rheumatic fever for about two months and 2 had acute iritis. A history of an attack of acute tonsillitis shortly before the onset of the systemic disease was elicited in each of these cases, and large amounts of liquid pus were expressed from the tonsils of each by the method my colleagues and I use. Acute pulpitis with death of the pulp and draining dental sinuses occurred shortly before the attack in each of the 2 cases of acute iritis. And, finally, Schottmuller himself had been at home in bed ill with an unexplained fever for some time prior to my visit. It was clearly evident that he was an example of the very problem under discussion. His teeth were literally floating in pockets of pyorrhea, and his breath was terrible. He died several years later of cardiac failure.

In regard to Reimann's criticism of the work which Heilman and I<sup>2</sup> have done on the prevention and treatment of colds and influenza, I am impelled to record the following statements. It is generally conceded, as indicated in our paper, that the initial symptoms in colds and influenza are associated with the virus and that

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1 Reimann, H. A. Infectious Diseases. Review of Current Literature, *Arch Int Med* 62 305-352 (Aug) 1938.

2 Rosenow, E. C., and Heilman, F. R. Streptococcal Vaccines in the Prevention and Treatment of Respiratory Infections, *Am J Clin Path* 8 17-27 (Jan) 1938.

organisms of the pneumococcus-streptococcus group are the chief cause of the subsequent symptoms, lesions, complications and death. The strains of these organisms from persons having colds or influenza possess on isolation characteristic pneumotropic virulence and other specific properties which they promptly lose on cultivation on artificial mediums. They become like the strains isolated from the throats of well persons remote from an epidemic of infections of the respiratory tract<sup>3</sup>. In previous work<sup>4</sup> the value of vaccines prepared from freshly isolated strains of this group of organisms was demonstrated in animals and on a large scale in human beings during the pandemic of influenza of 1918 to 1920. The vaccinated patients as compared with the unvaccinated controls fared from three to twelve times better as regards the rate of attack, incidence of pneumonia, hemorrhagic edema of the lungs, empyema and encephalitis. It seems (1) that Reimann overlooked the fact that our results obtained in human beings, especially in prevention, were so overwhelmingly favorable whenever the vaccine was used as to leave no doubt of its value, (2) that the vaccine actually used for human beings protected animals against infection by streptococci regularly at hand in these diseases, (3) that he failed to consider the fact that our vaccine was prepared from strains freshly isolated in dextrose brain broth after preservation in dense suspension of glycerin (two parts) and 25 per cent salt solution (one part), that vaccines prepared in this way are much less toxic and more immediately antigenic and hence more suitable for treatment than vaccines prepared directly in the usual manner from streptococci, often after almost indefinite cultivation on artificial mediums, and (4) that he seems to have missed completely the remarkable fact that a vaccine prepared in 1937 from four hundred strains of streptococci isolated during the pandemic of 1918 to 1920 and preserved in the glycerin-salt solution menstruum protected animals against the streptococcus isolated from persons ill with influenza during an epidemic in 1937. This vaccine was not used for human beings, as stated by him, but instead vaccines prepared from a number of more recently isolated strains.

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3 Rosenow, E. C. Cataphoresis as a Control of Specificity of Streptococcal Vaccines. Influenzal Streptococcus Vaccine in the Prevention and Treatment of Infections of the Respiratory Tract, *J. Immunol.* **26** 401-433 (May) 1934.

4 Rosenow, E. C. Studies in Influenza and Pneumonia. IV. Further Results of Prophylactic Inoculations, *J. A. M. A.* **73** 396-401 (Aug 9) 1919.

## News and Comment

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### NEWS AND COMMENT

American Board of Internal Medicine, Inc.—Written examinations for certification by the American Board of Internal Medicine will be held in various sections of the United States on the third Monday in October 1939 and the third Monday in February 1940

Formal application must be received by the secretary before Aug 20, 1939 for the examination on Oct 16, 1939, and on or before Jan 1, 1940 for the examination on Feb 19, 1940

Application forms may be obtained from Dr William S Middleton, secretary-treasurer, 1301 University Ave, Madison, Wis

## Book Reviews

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Investigations on Epilepsy and Water Metabolism By H P Stubbe  
Teglbjaerg Pp 247 Copenhagen Levin & Munksgaard, 1936

In this monograph Teglbjaerg reports the results of studies on the metabolism of water in cases of epilepsy and the effects of variations in the intake of water on the frequency of seizures. The work was done in the Filadelfia colony for epileptic patients in Dianalund, Denmark. The author assumes that there is a dualistic pathogenesis of epilepsy—a "cerebral factor," in the form of a disease of the brain, and a "humoral factor" of constitutional origin, resulting in a lowered threshold for convulsions. In cryptogenic epilepsy the cerebral factor is not demonstrable, but its presence must be assumed, chiefly by analogy. The arguments for the humoral factor include the precipitation of seizures by hyperventilation in a high percentage of cases, the failure of trauma and tumors to produce epilepsy in many cases and the tenfold greater frequency of epilepsy among relatives of epileptic patients than among "normal" persons. To these arguments Teglbjaerg adds the beneficial effects of a ketogenic diet, inanition and dehydration.

The studies on which the monograph is based include an investigation of the water balance of normal and of epileptic subjects. Attention was paid not only to the free water administered to the patients but also to the constitutional and oxidation water of the food, which represents about one-half the amount available to the subjects. The balance of sodium chloride was also studied, as well as the effects of various diuretics and the antidiuretic pitressin. The "spontaneous water balance" was found to be more unstable in epileptic than in normal persons, but no relation was discovered between the seizures and the spontaneous retention of water or changes in the volume of blood. The frequency of seizures was lowered but not abolished by dehydration and was increased by hydration. Extensive and careful studies of insensible perspiration failed to yield any significant information as to the water regulation of the organism, either in normal or in epileptic persons. The pressure of the cerebrospinal fluid was likewise found to be normal between seizures in epileptic patients and to be practically unaffected by the injection of physiologic or hypertonic solutions of sodium chloride or dextrose. Others have shown, however, that hyperhydration plus the antidiuretic effect of pitressin does increase the cerebrospinal fluid pressure.

Teglbjaerg concludes from his studies that though the frequency of seizures in epileptic patients is increased by hydration and decreased by dehydration, there does not appear to be any gross change in the water balance or in the cerebrospinal fluid pressure which might explain the seizures. He thus discards completely the mechanical pressure theory of Temple Fay as being unsupported by the facts. He adheres rather to the view of McQuarrie that an important part of the constitutional factor in epilepsy is a disturbance in the cellular susceptibility to hyperhydration. He thinks that this susceptibility may be an altered permeability of the cell membrane, especially since disturbances have been found in the lecithin-cholesterol quotient of the blood of epileptic patients and since these lipoids have a great influence on the permeability of the cell membrane. He states, however, "It will be a question of words rather than of realities whether one wishes to ascribe the epileptic seizures to a sudden change in the surface tension of the cell, or in the ion milieu of the cell."

This work of Teglbjaerg, amply documented with charts and graphs, represents an important contribution to an understanding of the intimate nature of epilepsy. His facts, which seem securely established, are nevertheless not yet easy to incorporate in a consistent theory of epilepsy. An excess of water is not the only factor

that will precipitate seizures in epileptic patients, nor will it serve to bring them on in all such patients. While many epileptic patients are sensitive to hydration, that is not equivalent to saying that spontaneous seizures are due to a disturbance in the metabolism of water. In fact, Teglbjaerg's work in some respects seems to render this unlikely. On the other hand, a valuable therapeutic weapon is at hand in dehydration, properly carried out. Although an ultimate understanding of epilepsy appears almost as distant as ever, any thoroughgoing explanation must account for the role played by water in the causation of seizures. To such an explanation this monograph is an important preliminary.

**Oreille interne** Etude anatomo-pathologique et clinique, technique histologique et expérimentale. By C. Claoué. Second edition. Paris: Norbert Maloine, 1938.

Convinced that anatomy and biology constitute the foundation on which medical education—especially the training of the specialist—should be based, Dr. Claoué has written an instructive textbook on the internal ear. There is a short introductory chapter on development which leads to an account of maldevelopments met with in practice, as well as of the neurovascular pathways along which infection may spread from the ear to the subarachnoid spaces.

The main text is divided into three parts. The first deals with anatomic, pathologic and clinical considerations of the inner ear, the second, with the technique of microscopic examination, and the third, with a study of the ear of the guinea pig. In the first part the inner ear is described, region by region, in separate chapters, each being introduced by a short anatomic review. Thus the first chapter deals with the osseous capsule—its formation and its more common lesions—otosclerosis, rickets and Paget's disease. Then follows a chapter descriptive of the perilymph spaces, with a consideration of their invasion by infections, especially those associated with removal of granulations in the middle ear and of curettage of its medial wall. The chapter on the endolymph spaces contains a description of the degeneration in the membranous labyrinth which may accompany general diseases, such as leukemia and syphilis, as well as the pathologic picture of occupational deafness. This is followed by a chapter on the internal auditory meatus. The fifth chapter may be said to be a general summation of the four previous chapters. As an addendum the author has a chapter on the technique of opening the internal auditory canal from the middle ear and the operative treatment of labyrinthine meningitis.

This method of considering lesions of the inner ear makes the book of great value not only to the otologists but to the general practitioner who desires an understanding of the lesions met with in the course of his practice. The author is to be congratulated not only on this presentation but also on the numerous and apt illustrations which add to the clarity of the text.

**Hypervitaminosis D**, belyst gennem kvantitative overdoseringsforsøg. By Axel Guldager. Pp. 219, with 14 illustrations. Copenhagen: Nyt Nordisk Forlag, Arnold Busck, 1936.

This dissertation is concerned with the question of whether the poisoning produced by excessive doses of preparations of vitamin D is true hypervitaminosis or merely poisoning due to substances difficult to separate from the vitamin. The author is convinced that he dealt with true hypervitaminosis D in his experiments because preparations from three independent sources, when used on mice and rats, gave the following results. No qualitative difference was found in the symptoms produced by the three commercial preparations as compared with those produced by purified vitamin D. Quantitative comparison showed the toxicity to be proportional to the vitamin content, within the limits of experimental error. Doses which were harmless when given daily over short periods sometimes caused

typical symptoms of hypervitaminosis if continued for longer periods, but sufficiently small doses, of 1,400 to 1,500 U S P units per day, were continued for half a year without cumulative effects. Lack of vitamin A in the diet increased the sensitiveness of the animal to excess of vitamin D. Lack of vitamin B similarly increased the sensitiveness of rats to excess of vitamin D. Increasing the intake of vitamin B above its optimum did not protect against excess of vitamin D. Increasing the calcium in the diet increased the sensitiveness of mice to vitamin D so markedly that an otherwise harmless dosage of vitamin D was made markedly toxic thereby. The effect of phosphates was similar to that of calcium, though less marked. Gravid mice were unaffected by doses that had been found toxic for nongravid mice.

**The Vitamins and Their Clinical Application** By Dr Wilhelm Stepp, Dr Joachim Kuhnau and Dr Hermann Schroeder. Translated by Herman A. H. Bouman. Price, \$4.50. Pp 173. Milwaukee: The Vitamin Products Co., 1938.

The purpose of this small book is to give to the average physician a bird's-eye view of the rapidly developing field of vitamins. To write a concise review of a new and expanding field of science is an extremely difficult and nearly impossible task, since apparent and well established facts may become obsolete in a short time. The authors have done well in presenting this complicated subject in such a compact and simple manner. In many instances, seemingly dogmatic statements are made, obviously to carry the reader over a vast and contested experimental field. In discussing the therapeutic application of vitamin therapy the writers mention many instances in which reported benefits are based on only 1 or more case reports, and such statements may be misleading if one is not acquainted with the literature on the particular subject.

In all, this book should be very useful for one who wishes to obtain a rather quick and concentrated dose of "vitamin knowledge." The bibliography is adequate (one third of the book) but not complete, and a large number of the references are naturally to German articles. It is to be remembered that since this book went to press there has been considerable advance in knowledge of vitamins, such substances as nicotinic acid and vitamin K are conspicuous by their absence.

**Undersøgelser over calciumudskillelse** By Harald Christiansen. Pp 108. Copenhagen: Nyt Nordisk Forlag, Arnold Busck, 1936.

This excellent thesis contradicts, on the basis of painstaking work, the long-accepted idea that the intestinal tract is the excretory organ for calcium. After a review of the conflicting reports on the subject, the author presents his own experiments on rabbits and goats. Feces, urine, bile, milk and various organs were analyzed for calcium, and the calcium balance was studied during inanition, during periods in which diets low in calcium were given and during periods of slow, continuous intravenous injections of solution of calcium salts.

The results disclosed the existence of a slow, irregular loss of calcium by way of the gastrointestinal tract. The intravenous administration of calcium did not accelerate this loss and did not increase the amount of calcium in the bile. Neither did it accelerate the secretion of calcium in the milk. It did, however, increase the urinary output and the amount stored in the kidneys. The kidneys were the only organs except the bones that showed an increased calcium content after the injections. Other evidence corroborated the view that the kidneys govern calcium balance by regulating their output of the element. Fatalities during slow injections were found to be caused not by hypercalcemia directly but by excessive retention of the element in the substance of the kidneys, with consequent nephritis and uremia. This helps to explain the nephritis of hyperparathyroidism and hypervitaminosis D.

**A Monograph on Veins** By Kenneth J. Franklin, D.M., M.R.C.P., Tutor and Lecturer in Physiology, Oriel College, University Demonstrator of Pharmacology, Assistant Director of the Nuffield Institute for Medical Research Oxford Price, \$6 Pp 410, with 46 illustrations Springfield, Ill Charles C. Thomas, Publisher, 1937

This book is a rather attractive and readable exposition on veins from the standpoint of physiology. It contains a comprehensive and detailed review of the historical development of the knowledge of veins and their physiology. According to the author's statement, this book is primarily intended for those engaging in researches on the vascular system and the circulation of the blood. From the standpoint of the general student of the subject the amount of space devoted to the review of the literature on venous physiology seems a little too extensive, and an adequate summary is lacking. The chapter at the end of the book on clinical aspects is disproportionately brief, dismissing many interesting and controversial points too quickly. There is little in the book concerning the pathology and pathogenesis of lesions of the veins. Thus, to the reader who is interested solely in the diseases of the veins and their treatment the book may be somewhat disappointing. To the student who is interested in some problem in the physiology of the circulation it should be a valuable summary and reference guide.

**Undersøgelser over testis histopathologi ved E-avitaminose. En eksperimentel-morphologisk studie** By Axel Ringsted Pp 191, with 30 illustrations Copenhagen Nyt Nordisk Forlag, Arnold Busck, 1936

This dissertation contains a review of the subject of vitamin E and a presentation of the author's own experiments on the rat. The sterility caused by lack of vitamin E affects not only the female but the male. In the latter the gradual testicular degeneration was followed in great detail up to four hundred and sixty days after institution of the deficient diet. The earliest changes were in the seminiferous elements, but later the interstitial tissue also suffered extreme atrophy. The degeneration was never uniform throughout a testicle, even in a maximally deteriorated organ a few well preserved seminal tubules persisted. While some of these changes were nonspecific, others seemed to be diagnostic of lack of vitamin E and therefore possibly of use in the development of methods of assay. For any one who may undertake research on the antisterility vitamin, this book, with its excellent photomicrographs and its wealth of detail as to dietary and histologic technic, will be a prerequisite.

**The Compleat Pediatrician** By Wilburt C. Davison Second edition Price, \$3.75 Pp 274 Durham, N. C. Duke University Press, 1938

The "index of symptoms method" of writing a textbook has been somewhat discredited in the past, but Dr. Davison has overcome its defects and produced a really valuable compendium. The explanation of success in this case is not far to seek. The writer knows what he is talking about, the literature is thoroughly covered and the style has clearness, force and precision. As a *vade mecum* and an aid to quick orientation as to diagnosis and procedure, it should be (as the need for a second edition shows) invaluable not only to the pediatrician but to the general physician.

**Le traitement de la tuberculose pulmonaire par la tuberculine** By Dr. M. Jaquerod Price, 250 francs Pp 43, with 2 illustrations Lausanne Librairie Payot & Cie, 1937

This small pamphlet deals with tuberculin therapy as practiced by the author at present. It presents little or nothing that is new, and to the American reader it appears a bit optimistic. In spite of the case which is made out by the author, it is doubtful if this pamphlet will obtain many converts to tuberculin therapy in this country.

## TUBERCULOSIS OF THE TONSILS

ITS INCIDENCE AND ORIGIN

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Numerous reports have been made on the incidence of tuberculosis of the tonsils as determined by examination of large series of these organs obtained after tonsillectomies. Such studies have greatest significance when accompanied with a record of the clinical condition of each of the patients concerned, for the incidence varies according to the presence or absence of tuberculosis elsewhere in the body. It is now well known that many, if not most, patients with open pulmonary tuberculosis have tuberculosis of the tonsils. Hence a study of the incidence of tonsillar tuberculosis in a population group including many persons with open pulmonary tuberculosis yields an excessive rate for this disease in the tonsils. Conversely, a slight error is introduced if persons with open tuberculosis of the lungs are excluded, for persons with pulmonary tuberculosis make up not a negligible proportion of the population.

### REVIEW OF THE LITERATURE

These facts are readily apparent in a review of the literature on tuberculosis of the tonsils. Newhart, Cohen and van Winkle,<sup>1</sup> in a study of the single sections from tonsils of approximately 100 patients with the adult type of pulmonary tuberculosis, found tuberculosis in 48 per cent. This figure was below the true percentage, for examination of 20 of the "negative" pairs of tonsils by the laborious method

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<sup>1</sup> Newhart, H., Cohen, S. S., and van Winkle, C. Tonsillectomy in Tuberculosis. Incidence and Pathology of Tuberculosis of the Tonsil in Adults, *Ann Otol, Rhin & Laryng* 43:769, 1934.



of serial sections showed a fifth of them to be tuberculous. The indicated high rate was contrasted by the authors with the low rate of 1 per cent found in a study of 100 "healthy" persons. It is significant that the single patient who was responsible for the 1 per cent in this series formerly had pulmonary tuberculosis.

Other studies of this character need not be cited, as the one described is typical. What is most remarkable is that a pathologic state so common is rarely recognized clinically. This is not a reflection on the diagnostic capacity of the physicians examining the throats of tuberculous patients. Tuberculosis of the tonsils is rarely superficial and seldom extensive. Ordinarily it is detectable only on microscopic examination, and when found it is usually submucosal and at the bottom of a crypt. In the clinic at the Henry Phipps Institute approximately 500 patients with active tuberculosis of the adult type are seen annually, all of whom are given careful examinations of the nose and throat, and although the majority of these patients have advanced pulmonary disease and presumably tonsillar tuberculosis also—judging from the figures just recorded—tuberculosis of the tonsils is almost never recognized macroscopically.

The importance of a correlated clinical study is well brought out in the recent report by Urbantschitsch.<sup>2</sup> In examination of 1,000 pairs of tonsils that had been removed because of hypertrophy or other abnormality of the lymphatic structures of the throat, 14 cases of microscopic tuberculosis were found. Roentgen examination of the chests of 13 of the 14 patients concerned revealed obvious or probable tuberculosis of the lungs in almost every one. In 2 advanced pulmonary disease was present, while the rest showed the calcified or fibrotic nodes and nodules of old tuberculosis of the childhood type or the broad shadows of the hilus of the lung and the small infiltrations of still active pulmonary tuberculosis.

It is significant that with the decrease in the incidence of tuberculosis in the general population the incidence of tuberculosis in removed tonsils is also declining. The reports from the University of Michigan, based on an abundance of material, are illuminating in this respect. Weller,<sup>3</sup> in 1921, reported an incidence of 2.5 per cent in 8,697 pairs of tonsils within the preceding thirteen years. Magee,<sup>4</sup>

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2 Urbantschitsch, E. Ueber Tuberkulose des Rachenringes und dessen Erkrankung bei Tuberkulosen, *Monatschr f Ohrenh* **71** 1096, 1937.

3 Weller, C. V. The Incidence and Histopathology of Tuberculosis of the Tonsils, Based on Eight Thousand and Six Hundred Tonsillectomies, *Arch Int Med* **27** 631 (June) 1921.

4 Magee, M. C. The Changing Incidence of Tuberculosis of the Tonsils, *Arch Int Med* **59** 445 (March) 1937.

in 1937, brought the study up to date by reporting on 6,359 pairs of tonsils examined in the same laboratory in the intervening years. The incidence had dropped to 0.44 per cent, and the decrease was apparent in all age groups.

From this large volume of material, obtained without deliberate selection with respect to inclusion or exclusion of tonsils from patients with known tuberculosis of other parts of the body, Weller was able to generalize on the source and character of the tonsillar disease. Three types were recognized: (1) focal cryptic tuberculosis, (2) ulcerative and more massive disease and (3) diffuse bilateral follicular involvement. The focal cryptic type was encountered frequently in cases of open pulmonary tuberculosis, and the more extensive ulcerative lesions apparently resulted from massive coalescence of tuberculous tissue of focal cryptic origin. The diffuse form, follicular and usually bilateral, appeared to be merely one expression of generalized tuberculosis after invasion of the blood stream.

In the majority of cases, however, the disease detected was focal, cryptic and monotonsillar. Weller expressed the belief that its character spoke for primary infection, and he noted that it was seen with particular frequency in nurses, hospital interns and advanced medical students—in other words, in a group with more than ordinary exposure to casual tuberculous infection. He pointed out that the figures given on the incidence of tonsillar tuberculosis were probably far below the true incidence, for they were based on examination of single sections, and scars, which might have represented healed tuberculosis, were not included. Weller expressed the opinion that if it were possible to obtain a perfect record of past and present tonsillar tuberculosis the disease would be found as common as the scars of old pleural or pulmonary tuberculosis.

Most investigators who have dealt with the subject have attempted to make a distinction between primary and secondary tuberculosis of the tonsils. Rossner<sup>5</sup> distinguished them logically as follows:

1 Primary. Exogenous, by way of (a) inspired air or (b) the alimentary canal.

2 Secondary. Endogenous, by way of (a) the blood stream, (b) the lymph or (c) sputum.

Widely varying opinions have been expressed on the comparative frequency of tonsillar infection from these different sources. Rossner herself stated the belief that the tonsillar disease was usually secondary and the result of dissemination by the blood stream from a tuberculous focus elsewhere in the body, and she wrote that this was the view held

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5 Rossner, T. Häufigkeit und Bedeutung der Tonsillentuberkulose, Arch. f. Ohren-, Nasen- u. Kehlkopfh. **135**: 214, 1933.

by most authors Libin and Travushkina,<sup>6</sup> who recently reported on a large series of cases, came to the same conclusion but stated that most authors believe the tonsils of patients with pulmonary tuberculosis become infected through the sputum These two references are sufficient to indicate the wide difference of opinion

As indicated before, the question of primary or secondary localization in the tonsils can be settled only in the light of complete knowledge of the condition of the rest of the body, and this degree of knowledge is almost impossible to attain Hence, although many investigators, like Weller, have considered primary tuberculosis of the tonsils extremely common, proof that such infection is primary is rare Ghon<sup>7</sup> and his associates in their exhaustive study of the primary focus of tuberculosis concluded that primary tuberculosis of the tonsils is exceedingly infrequent The requirement for a diagnosis of a primary focus in the tonsil was set as the presence of a typical primary complex, with disease in the tonsil and in the regional lymph nodes and with absence of tuberculosis elsewhere in the body—conditions obviously to be established only by exhaustive postmortem study In spite of these difficult criteria he was able to cite a few cases Other cases that appear to satisfy the requirements have been recorded more recently (Suve,<sup>8</sup> Hamperl and Wallis<sup>9</sup>), and in one of these cases<sup>8</sup> infection through a contaminated object, a rubber nipple moistened with sputum, seemed definitely probable

In spite of the apparent rarity of primary tonsillar tuberculosis, as determined by necropsy, the opinion is still widespread that the tonsils may serve as a portal of entry for tubercle bacilli, and indeed the view once expressed by Aufrecht,<sup>10</sup> that the most important portal of entry for tubercle bacilli in the human body is the tonsil, has not altogether been abandoned The early views of Behring and Calmette on the portal of entry in tuberculosis are well known In France especially, owing to the influence of Calmette, the alimentary portal

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6 Libin, S I, and Travushkina, M V Tuberculosis of the Tonsils, *Probl tuberk*, 1937, no 10, p 67, abstracted, *J A M A* **110** 1154 (April 2) 1938

7 Ghon, A, and Kudlich, H Die Eintrittspforten die Infektion vom Standpunkt der pathologische Anatomie, in Engel, S, and von Pirquet, C *Handbuch der Kindertuberkulose*, Leipzig, Georg Thieme, 1930, vol 1, p 20

8 Suve, S A Die Tonsillen als Eintrittspforten für Tuberkelbacillen in Kindesalter, *Beitr z Klin d Tuberk* **82** 279, 1933

9 Hamperl, H, and Wallis, K Ueber primäre Tonsillartuberkulose, *Ztschr f Hals-, Nasen- u Ohrenh* **32** 480, 1933

10 Aufrecht, E Die Genese der Lungenphthisie und die Verschiedenheit der mit den Namen Tuberkel bezeichneten Gebilde, *Deutsches Arch f klin Med* **75** 193, 1903

is stressed Calmette, Boquet and Nègre<sup>11</sup> pointed with particular emphasis to the possibility of primary absorption of tubercle bacilli from the mouth and pharynx as well as from the intestinal tract

Montmollin<sup>12</sup> stressed the discoveries in the Lubeck disaster and recalled the well known experiments<sup>13</sup> in which rapid absorption from the tonsils and wide dissemination in the body resulted from experimentally placing minute particles of pigment and other foreign material on the tonsils. Certainly the Lubeck tragedy indicated clearly enough that primary involvement of the tonsillar ring may occur. Of the children dying in this unintentional experiment in massive infection 78 per cent showed the structures of the throat and neck involved (Schurman<sup>14</sup>). The primary infection, it should be noted, was usually multiple, being single in only a few of the infants, and double, triple or quadruple in the rest.

An association between tuberculosis of the tonsils and tuberculosis of the cervical lymph nodes seems clearly established. MacCready and Crowe,<sup>15</sup> while noting tuberculosis of the tonsils in less than 2 per cent of patients without clinical tuberculosis, found lesions in the tonsils in 48 per cent of patients with tuberculous cervical lymphadenitis. Montmollin<sup>12</sup> found tonsillar tuberculosis in 9 of 100 patients from Rollier's sanatorium in Leysin, and in 2 it was associated with disease of the cervical lymph nodes. Schlittler,<sup>16</sup> in 1934, reported tuberculous tonsils in 98 patients with tuberculosis of the cervical lymph nodes. At that time he considered the tonsils the portal of entry, but recently, as a result of study of a second series<sup>17</sup> of 41 patients with tuberculous cervical lymphadenitis, he came to a different conclusion. In every one of the latter the tonsils were tuberculous, and the infection was usually bilateral. As a result of this finding he expressed the belief that the tonsillar disease in both series was hematogenous.

From the foregoing citations it is apparent that the status and the importance of primary tuberculosis of the tonsils are still uncertain.

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11 Calmette, A. *L'infection bacillaire et la tuberculose chez l'homme et chez les animaux*, ed 4, revised by A. Boquet and L. Nègre, Paris, Masson & Cie, 1936.

12 de Montmollin, C. *Amygdales et adénoïdes, porte d'entrée de la tuberculose chez l'enfant?* *Schweiz med Wchnschr* **15** 442, 1934.

13 For a review of the experiments mentioned see Weller<sup>3</sup> and Calmette<sup>11</sup>.

14 Schurman, P. *Beobachtungen bei den Lubecker Säuglingstuberkulosen*, *Beitr z Klin d Tuberk* **81** 294, 1932.

15 MacCready, P. B., and Crowe, S. J. *Tuberculosis of the Tonsils and Adenoids. A Clinical and Roentgen-Ray Study of Fifty Cases Observed for Five Years After Operation*, *Am J Dis Child* **27** 113 (Feb.) 1924.

16 Schlittler, E. *Ueber die Bedeutung der Tonsillen als Eintrittspforte der Tuberculose*, *Schweiz med Wchnschr* **64** 594, 1934.

17 Schlittler, E. *Zur Frage der "primären" Mandeltuberculose*, *Schweiz med Wchnschr* **68** 42, 1938, abstracted, *J A M A* **110** 773 (March 5) 1938.

It is clear that tonsillar involvement secondary to open pulmonary tuberculosis is common, but it is usually a relatively small matter as compared with the pulmonary disease. Tonsillar infection is also common in association with tuberculosis of the cervical lymph nodes, and it would seem most plausible to consider the nodes as involved secondarily to the tonsils, as with any other portal of entry and its tributary lymph nodes. But doubt has been cast on their view.

Finally, slight tuberculosis of the tonsils has been reported as common, and probably representative of primary infection, in persons without clinical evidence of tuberculosis elsewhere. It has been indicated that such infections are prone to heal and to leave little or no local trace. MacCready and Crowe<sup>15</sup> followed a number of patients with such infections over a period of years and came to the conclusion that there is no great likelihood of the development of tuberculosis elsewhere as a result of this entrance of tubercle bacilli.

A number of authors (especially Newhart, Cohen and van Winkle,<sup>1</sup> Rossner,<sup>5</sup> Libin and Travushkina,<sup>6</sup> Schlittler,<sup>17</sup> MacCready and Crowe,<sup>15</sup> Pinkerton<sup>18</sup> and Hudson and Wollaston<sup>19</sup>) have discussed the danger of tonsillectomy in patients with tuberculosis of the tonsils. The general view expressed is that the operation exposes the patient to no undue hazard of spread of the tuberculosis but rather reduces symptoms caused by absorption from tuberculous foci.

It will be seen from the preceding review that two of the most contested problems are (1) whether the small tubercles often found in the tonsils in the absence of demonstrable pulmonary tuberculosis represent primary, or at least exogenous, tuberculosis and (2) whether the tonsillar tuberculosis found so frequently in the presence of pulmonary tuberculosis is hematogenous or is derived from infected sputum.

#### MATERIAL

The investigation reported here was undertaken in the hope that study of a large number of tonsils removed from children in regions of high tuberculous morbidity and bad hygienic conditions might throw light on these questions. The highest mortality rates for tuberculosis in the United States are said to prevail in the Indian population of the West. Although the officially recorded rate for all Indians in the United States (except for certain agencies not reporting) is given as about 250 per hundred thousand persons (Korns<sup>20</sup>), it is recognized

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18 Pinkerton, F. J. Tonsillectomy in the Tuberculosis Patient, *Tr Am Laryng, Rhin & Otol Soc* **41** 540, 1935.

19 Hudson, B., and Wollaston, F. L. A Case of Massive Tuberculosis of the Tonsils, *Tubercle* **17** 30, 1935.

20 Korns, J. H. Comparative Tuberculosis Findings Among Indians and White Persons in Cattaraugus County, New York, *Am Rev Tuberc* **34** 550, 1936.

that the official records are often inaccurate, and it is commonly believed that on those reservations where the Indians still follow their more primitive customs the true rate is much higher. The mortality rate for tuberculosis in Montana for the period from 1925 to 1930 has been given as 775 (Warner<sup>21</sup>), with rates as high as 1,300 in some areas (Crouch<sup>22</sup>). An estimate of about 800 was reported recently for one area in the Southwest on the basis of a survey for tuberculosis (Long and Hetherington<sup>23</sup>), and a rate of 409 for the years from 1927 to 1931 was recorded in Minnesota (Burns<sup>24</sup>). Most physicians in the Indian service of the United States would probably consider an estimate of about 600 per hundred thousand conservative for large parts of the western reservations.

Since the physicians in the Indian field service annually perform tonsillectomy on large numbers of patients, it seemed to us that an opportunity was present for studying the question of primary oral infection. By permission of the Office of Indian Affairs and with the cooperation of physicians in the field service, 1,000 pairs of tonsils from Indian children and young adults were secured for examination. More than a third of the specimens were from Navajos. Tuberculosis is common in this tribe, where living conditions are exceptionally primitive, crowding in the home customary, and sputum contamination of the floor and of the household articles frequent. In such conditions buccal infection as well as infection by inhalation might well be expected. The rest of the tonsils were obtained from Blackfeet, Apache, Chippewa, Cherokee, Sioux, Papago, Creek, Paiute and other tribes.

As the study progressed much tonsillar tuberculosis was found, and it seemed wise to collect tonsils from regions with a lower tuberculosis morbidity rate for comparison. The mortality rate for tuberculosis in Puerto Rico, though notoriously high, is much lower than the rates believed to prevail on most Indian reservations, and opportunity was at hand to study tonsils from this source also. Six hundred pairs of tonsils were obtained from patients in three hospitals in San Juan. Finally, through the cooperation of the staffs of the Pennsylvania and the Mount Sinai Hospital, a set of 400 pairs was secured for comparison from Philadelphia, where the mortality from tuberculosis is only slightly higher than that in the United States as a whole. This series, as it turned out, in view of the small amount of tuberculosis found, was

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21 Warner, H. J. The Incidence of Tuberculous Infection Among School Children on Five Montana Indian Reservations, *Am Rev Tuberc* **26**:507, 1932.

22 Crouch, J. H. A Study of Tuberculosis Among the Indians in Montana. Preliminary Report, *Pub Health Rep* **47** 1907, 1932.

23 Long, E. R., and Hetherington, H. W. A Tuberculosis Survey in the Papago Indian Area of Southern Arizona, *Am Rev Tuberc* **33** 407, 1936.

24 Burns, H. A. Tuberculosis in the Indian, *Am Rev Tuberc* **26** 498, 1932.

too small to be of equal statistical significance with the series obtained from the Indian reservations and Puerto Rico

By original intention the study was limited to tonsils from patients in whom tuberculosis of the lungs was not known to exist, but in the large series from the Indian service a small number of pairs of tonsils from patients known or suspected to have pulmonary tuberculosis were included, and this was true also of a few pairs of tonsils from Puerto Rico

Blocks of tonsil were fixed in a 5 per cent solution of formaldehyde, and single sections or ribbons of two or three sections were mounted and stained with hematoxylin and eosin. Whenever in the hematoxylin and eosin sections characteristic tubercles were found, stains for acid-fast bacilli were made

#### INCIDENCE OF TONSILLAR TUBERCULOSIS

Table 1 summarizes the results for the three groups (as noted, the tonsils of Indians came from widely scattered areas). Tuberculosis

TABLE 1—*Comparison of the Incidence of Tuberculosis in Tonsils Removed in Communities of Varying Tuberculosis Mortality*

Source of Tonsils	Approximate Tuberculosis Mortality Rate per 100,000 in the Community in 1937	Average Age of Patients, Years	Pairs of Tonsils Examined	Tuberculous Tonsils	
				Number	Per Cent
Indian reservations	About 600	13.5	1,000	65	6.5
Puerto Rico	200	15.9	600	15	2.5
Philadelphia	60	12.0	400	1	0.25
Total Average		14.0	2,000	81	4.2

was discovered in one of both tonsils in 81 patients. The rate of tonsillar infection among Indians was by far the highest, that among Philadelphians low, representing only 1 case, while that among Puerto Ricans was intermediate. Only tonsils with tubercles that were histologically characteristic are included in the figures given. Considerable scarring, with good evidence of healing, was found in many of the tonsils showing frank tuberculosis, and similar scarring without definite tuberculosis was occasionally found in other specimens, leading us to suspect a tuberculous origin. The latter specimens, however, are not included as tuberculous in the record.

#### ORIGIN OF TONSILLAR TUBERCULOSIS

It was obviously impossible to tell from histologic examination of the tonsils whether the infection was primary or secondary, exogenous or endogenous. It was possible, however, to learn something of the

clinical condition of the patients from whom the tuberculous tonsils were obtained. In every case an attempt was made to secure a roentgenogram of the chest. This proved possible in 35 of the 81 cases. In the majority of these 35 cases several weeks, and in some cases a few months, elapsed before the roentgenogram could be secured, as both Indians and Puerto Ricans often returned to distant homes after their brief stay in the hospital and were difficult to locate. In a few cases, fortunately, roentgenograms made just before tonsillectomy was performed were available. These were at hand either through hospital routine or as a sequel to surveys for tuberculosis in the area. Table 2 summarizes the distribution of the 35 cases in which a roentgenogram of the chest was available according to the indicated condition of the lungs.

It is significant that in approximately half the cases (18 of 35) active pulmonary tuberculosis of either the childhood or the adult type was revealed by the roentgenogram. In about two thirds of these

TABLE 2—*Distribution of Cases of Tonsillar Tuberculosis According to the Condition of the Lungs as Interpreted from Roentgenograms of the Chest*

Condition of Lungs	Cases of Tonsillar Tuberculosis
Apparently normal	9
Calcified primary tuberculosis only	2
Apparently normal, but cervical lymph nodes tuberculous	2
Apparently normal, but spine tuberculous	1
Childhood type of tuberculosis, regressing	3
Childhood type of tuberculosis, active	2
Adult type of tuberculosis, minimal	4
Adult type of tuberculosis, moderately advanced	5
Adult type of tuberculosis, far advanced	7
Total	35

cases, when the tonsils were reported to physicians of the Indian service as tuberculous it was learned that pulmonary tuberculosis had been known or suspected to be present. In the remainder of the 35 cases the discovery of the disease in the tonsils was the first evidence leading to its detection in the lungs. In most of the cases of active pulmonary tuberculosis it is probable that the sputum was positive, either constantly or intermittently, although presumably in the cases of the childhood type and of the adult type of minimal extent the number of bacilli expectorated was small. In the 3 cases of the childhood type in which the lesions were regressing it is possible that the sputum was still positive or had recently been positive for tubercle bacilli, but in the remaining 14 cases the roentgen appearance of the lungs was such as to suggest that they could not have discharged tubercle bacilli. Admittedly, minute lesions might have escaped detection.

In 3 of the 14 cases with sputum presumably negative for tubercle bacilli tuberculosis was known, either from the roentgenogram or from



an accompanying clinical history, to be present in another part of the body. In 2 of these cases, those of tuberculosis of the cervical lymph nodes, a lymphatic connection is obvious, although it was not directly evident in which organ the disease was precedent. This question has already been discussed. In the third case, that of tuberculosis of the spine, the connection might have been through the blood stream or through unrecorded additional tuberculosis in the lymphoid structures close to the tonsils. Subsequent examination did indeed show slight general enlargement of the cervical lymph nodes.

In another 2 of the 14 cases, although there was no evidence of active tuberculosis in the chest, signs of obsolete tuberculosis were present. For the other 9 cases, no record of tuberculosis in any part of the body was obtained, although it is possible that thorough clinical search might have uncovered a tuberculous focus—for instance, in the external lymph nodes—from which hematogenous or lymphogenous spread might have occurred. There is as good reason, however, to consider exogenous infection.

In the absence of any proof to the contrary, therefore, primary tuberculosis of the tonsils must be considered a possibility in the 9 cases in which the roentgenogram of the chest was negative for tuberculosis and in which no tuberculosis was detected in the clinical examination made at the time the roentgenogram was taken. Indeed, it is equally likely that the tuberculosis of the tonsils found in the 2 cases with no other evidence of pulmonary disease than calcified nodules was also primary in the sense that it was exogenous and independent of tuberculosis elsewhere in the body. Although the point is still disputed, there is increasing evidence that such tubercles do not serve as foci for the dissemination of bacilli. Furman's case,<sup>25</sup> recently described, might fall in this group. In all 11 cases the tuberculosis of the tonsils was slight as compared with that seen in the tonsils in cases of known tuberculosis. In most cases it consisted of a few epithelioid tubercles deep in the tonsil, in some cases only a single epithelioid tubercle was found. Among the latter was the case of a girl who originally was thought to have pulmonary tuberculosis and who was kept in the ward of a sanatorium for observation. No pulmonary tuberculosis was found, however, in roentgenograms taken before and after the tonsillectomy. It is possible that this was a case of primary tonsillar infection acquired in a roomful of patients with tuberculosis.

The deep location in the gland, commonly noted, while consonant with hematogenous development of the lesion from an unknown source, is not incompatible with the hypothesis of primary infection. Minor

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25 Furman, M. H. Primary Ulcerative, Infiltrative Tuberculosis of the Tonsils, *Ann Otol, Rhin & Laryng* 46: 456, 1937.

nontuberculous erosions through which tubercle bacilli could have entered were extremely frequent in the tonsils of this series, and the crypts were usually full of large and small leukocytes which could have carried bacilli into the gland in the course of their wandering

It is to be noted that the 11 patients who had tonsillar tuberculosis without any other known tuberculosis except the obsolete disease indicated by calcified nodules were much younger than those with tuberculosis of the tonsils in association with active pulmonary tuberculosis. The average age of the former group was 11 years. The average was 17 years in the group with frank tuberculosis of the adult type. This may have no further significance than the fact that an association with open pulmonary tuberculosis could hardly occur before adolescence, because of the relative rarity of this type of disease before that period.

There was little reason on the basis of the histologic lesions observed to believe that the tuberculosis of the tonsils found in association with frank pulmonary tuberculosis of the adult type was hematogenous. Repeatedly the tuberculous process was seen to extend from a number of crypts into the depths of the gland. It could have been argued that this apparent cryptal invasion might in reality be an erosion of the cryptal epithelium by a process extending from below, but the fact that erosion of the rest of the epithelial surface by underlying tubercles was rare made this seem unlikely. Therefore it was believed that the frequent tuberculous involvement of the crypts resulted from without, presumably from sputum that lodged and remained within the crypts. Corroborative evidence was not obtained, however, by finding sputum containing tubercle bacilli within the crypts.

Moreover, a direct test of the hypothesis of origin through sputum by examination of the tonsils of a group of patients with pulmonary tuberculosis whose sputum was supposedly free from bacilli, as determined by repeated examinations, brought out no difference from the group whose sputum contained tubercle bacilli. Through the cooperation of the staff of the Winslow Indian Sanatorium it was possible to examine the tonsils and study the roentgenograms of a group of patients, not recorded in tables 1 and 2, whose sputum had never shown bacilli or had apparently become free from the organisms in the sanatorium either through the application of pneumothorax or through spontaneous favorable progression. Protocols for 5 patients follow.

#### REPORT OF CASES

CASE 1—V L, a Navajo woman 23 years old, had bilateral pulmonary tuberculosis, moderately advanced. Bilateral pneumothorax brought steady improvement. The sputum was positive on Jan 20, Jan 27, March 4 and Aug 31, 1937, and was negative on Dec 14, Dec 17, Dec 18 and Dec 22, 1937, and on Jan 18, Feb 19, Feb 21, April 4 and May 31, 1938. Tonsillectomy was performed on

April 26, 1938 Extensive tuberculosis of both tonsils was revealed It may be pertinent to note that when a child this woman had a suppurative cervical lymph node, which had discharged and healed At the time of the tonsillectomy, however, there was no evidence of active tuberculous disease of the cervical lymph nodes

CASE 2—K T, a Paiute man 19 years old, had bilateral pulmonary tuberculosis, moderately advanced Pneumothorax on the right resulted in steady favorable progression The sputum was negative on Jan 1, Feb 24, April 4 and May 30, 1938 After tonsillectomy on April 13, 1938, both tonsils were found tuberculous In this case examination of the neck revealed no evidence of past or present tuberculosis of the cervical lymph nodes

CASE 3—H A, a Navajo woman 24 years old, had bilateral pulmonary tuberculosis, minimal in extent Favorable progress was made without pneumothorax The sputum was negative on Aug 11, 1937, and on Feb 14, April 2, May 5, June



Fig 1—Extensive tuberculosis of the margins of a tonsillar crypt in a patient (K T) with far advanced pulmonary tuberculosis

10, June 14 and June 18, 1938, it was positive, with a few bacilli, on June 12, 1938 Tonsillectomy was performed on April 26, 1938 Extensive tuberculosis was seen in both tonsils There was no evidence, on examination of the neck, of present or past tuberculosis of the cervical lymph nodes

CASE 4—G W, a Navajo woman 19 years old, had bilateral pulmonary tuberculosis, minimal in extent Pneumothorax gave steady slow improvement There was a history of tubercle bacilli in the sputum during a previous residence in another sanatorium The sputum was negative on May 5, May 17, May 18, Aug 26, Aug 31, Sept 25 and Sept 28, 1937, and on Feb 24, May 4, June 12 and June 14, 1938 After tonsillectomy on April 26, 1938, one tonsil was found tuberculous On examination of the neck no evidence of past or present tuberculosis of the cervical lymph nodes was found

CASE 5—T S, a Navajo girl 13 years old, had unilateral pulmonary tuberculosis of the childhood type, moderately advanced. There was favorable progression, with scarring. The sputum was negative on April 23, April 24, April 30, May 1, May 3 and Aug 30, 1937, and on Feb 1 and April 22, 1938. Tonsillectomy was performed on April 13, 1938, a few tubercles were found in one tonsil. On July 5, 1938, a small grayish white spot was seen on the faucial mucous membrane at the site of the left tonsil, and one lymph node seemed slightly enlarged in the left cervical tissues.

Protocols need not be given for a group of tuberculous patients in the same sanatorium whose cases were studied in connection with the 5 cases just summarized. All of these had positive sputum, and a few had tuberculosis of the cervical lymph nodes. The tonsils of all were tuberculous. It is of interest, however, to note that tuberculosis of the tonsils was not found in 1 case of advanced pulmonary tuberculosis in which the sputum was negative. The protocol follows.

CASE 6—N T, a Navajo woman 23 years old, had unilateral pulmonary tuberculosis, moderately advanced, with extensive fibrous pleuritis. Though no collapse of the involved lung was induced, there was steady favorable progression. The sputum was negative on July 22, July 23 and July 30, 1937, and on Feb 21, March 16, May 4, June 11, June 12 and June 14, 1938. After tonsillectomy on April 26, 1938, no tuberculosis was found in the tonsils. Examination of the cervical tissues on July 5, 1938, revealed nothing abnormal.

It will be evident that this limited study of special cases served only to emphasize the difficulty of demonstrating the route of infection in tuberculosis of the tonsils in cases of pulmonary tuberculosis. It might well be argued that the results speak for the hematogenous or lymphogenous route. On the other hand, examination of sputum by direct smear is far from perfect, and small numbers of bacilli may have been overlooked, although from the long series of negative results recorded it is evident that bacilli were at least rare in the sputum in the cases concerned here. Finally, in some of the cases the sputum was known to have been positive at an earlier stage of the disease, and the tonsillar disease in these cases may have had its origin in that earlier time.

The tuberculosis of the tonsils in the cases of apparent open pulmonary tuberculosis (table 2) was often of wide extent and associated with much scarring, suggesting heavy infection over a long period. This widespread character also argued against explanation of the disease on a hematogenous basis. While tubercle bacilli are known to be commonly present in the blood stream in advanced pulmonary tuberculosis and while evidence of invasion of the blood is frequent in the form of minute tubercles in the liver and spleen in cases in which death occurs from pulmonary tuberculosis, extensive tuberculosis of lymph nodes and viscera, comparable to the extensive tuberculosis found in these tonsils,



Fig 2—Epithelioid and fibroplastic tuberculosis of the tonsil in a patient (M R) with pulmonary tuberculosis of minimal but increasing extent

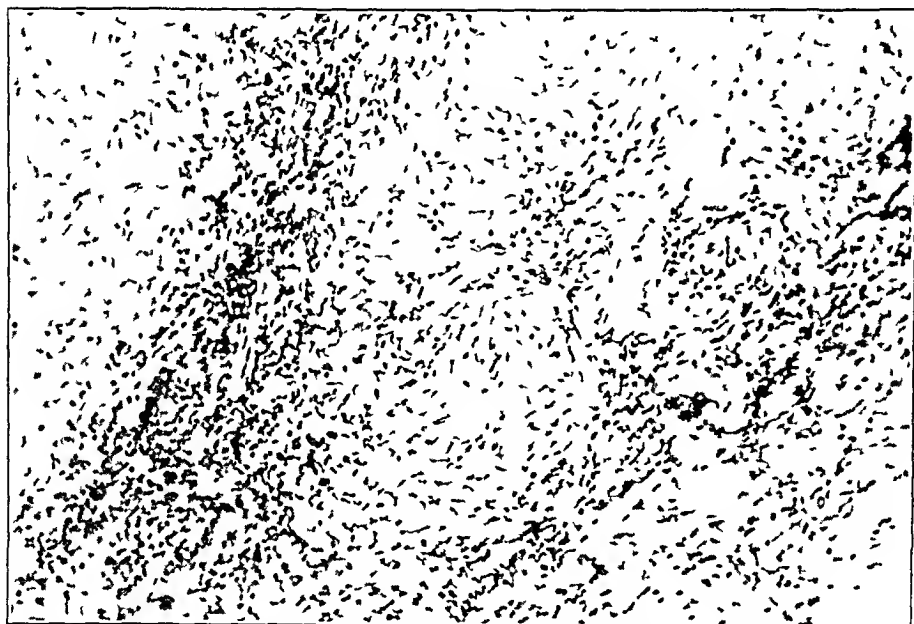


Fig 3—Regressing fibroplastic tuberculosis of the tonsil in a patient (S B) with chronic tuberculous cervical lymphadenitis

is rare. The widespread disease of the latter seems more readily explained, therefore, on the basis of frequent infection from bacillus-laden sputum.

In 75 per cent of the cases of tonsillar infection associated with pulmonary tuberculosis believed from the roentgenograms to be open, tuberculosis was discovered in both tonsils, as contrasted with 42 per cent of the total number of cases in which tuberculosis of the tonsils was discovered. As noted previously (Libin and Travushkina<sup>6</sup>), the predominance of bilateral involvement of the tonsils in cases in which there was associated pulmonary tuberculosis has been cited as evidence of a hematogenous source for the tonsillar disease. This seems an unwar-



Fig. 4—Single epithelioid tubercle, probably primary, in the tonsil of a patient (R. P.) with no clinical evidence of tuberculosis elsewhere in the body.

ranted deduction, however, for with the frequent passage of infected sputum through the mouth the opportunity for infection of both tonsils seems excellent.

On the other hand it may be significant that in 80 per cent of the cases of tonsillar infection not associated with tuberculosis elsewhere in the body only one tonsil was found infected. This is further evidence in favor of the view that the infection in these cases may have been primary. First infections are presumably caused as a rule by small numbers of tubercle bacilli as compared with the large numbers commonly present in the total daily output of sputum in cases of open tuberculosis. Correspondingly there would be a better chance for unilateral infection in the former than in the latter. Unilateral involvement

would also seem to point toward primary infection rather than to haematogenous dissemination, in which a fairly even distribution of bacilli over a long period might be expected. This, it will be recalled, is the view adopted by Weller.<sup>3</sup>

These suggestions must, however, be taken in the light of the fact that as a rule only one section of each tonsil was examined. Examination of serial sections or at least many sections from the same tonsil might have uncovered a larger percentage in which the disease was bilateral.

Acid-fast bacilli could be demonstrated in few cases and then only in minute number. This does not cast doubt on the tuberculous nature of the lesions so recorded. The histologic picture was characteristic, in more than half of the cases tuberculosis was present in another part of the body and finally, as is well known, tubercle bacilli are as a rule difficult or impossible to find in the epithelioid tubercles of lymph nodes.

#### SUMMARY

Two thousand unselected pairs of tonsils from routine tonsillectomies were sectioned and examined microscopically for tuberculosis. One thousand pairs came from various Indian reservations, known to be communities of high tuberculosis morbidity, 600 from Puerto Rico, a region with much tuberculosis, but of lower tuberculosis morbidity than the Indian reservations, and 400 from Philadelphia, a community of low tuberculosis morbidity in comparison with the other two.

Tuberculosis was found in 81 pairs of tonsils, including 65 per cent of the tonsils from the Indian reservations, 25 per cent of those from Puerto Rico and 0.25 per cent of those from Philadelphia.

Roentgenograms of the chest were secured in the cases of 35 of the 81 pairs. In 16 of these cases active pulmonary tuberculosis of the adult type was found and in 2 active tuberculosis of the childhood type. In general, the tonsillar lesions in this group were cryptal and were more extensive than those in the rest of the 35 cases, on the basis of pathologic appearance the tonsillar tuberculosis was believed to have resulted from direct infection by the bacilli contained in sputum from the associated pulmonary lesion. However, in a small series of cases of "closed" pulmonary tuberculosis in which the sputum was reported negative for tubercle bacilli over a long period and which were examined after the survey of 2,000 cases was completed, tonsillar tuberculosis was regularly found and was usually similar in character to that discovered in a corresponding number of cases in which the sputum was positive. Thus the mechanism of infection of the tonsils in cases of pulmonary tuberculosis remained unproved.

In 3 cases regressing tuberculosis of the childhood type was found in the roentgenogram, and in 3 cases the clinical record indicated that nonpulmonary tuberculosis was present

In 2 cases the roentgenogram of the chest revealed no abnormality other than calcified nodules from healed tuberculosis of the childhood type. In the remaining 9 cases no tuberculosis was apparent in the roentgenogram of the chest or in the accompanying clinical record. In these 9 cases the tuberculosis of the tonsils was probably primary, and in the 2 in which tonsillar infection was associated with calcified pulmonary lesions it is equally likely that the tonsillar lesion was exogenous. In most of these 11 cases the process consisted of a few epithelioid tubercles, and in 80 per cent of the cases the involvement was unilateral. This is in contrast to the observation in the cases of proved pulmonary tuberculosis, in which the tonsillar lesions were generally extensive and in 75 per cent of cases bilateral.

All stages of regression of tonsillar tuberculosis from active fibroplastic disease to scars indistinguishable from scars of other origin were seen in the series.

The relatively massive tuberculosis of the tonsils in cases of pulmonary tuberculosis, its tendency to be bilateral and its chronicity all point to repeated infection of these organs in the course of the pulmonary disease. Since all studies of tuberculosis of the tonsils show that tonsillar involvement occurs in a large proportion of cases of pulmonary tuberculosis, and since small tubercles tend to regress, there is reason to believe that at some time or other in the course of the disease the great majority of patients with progressive pulmonary tuberculosis, if not all of them, have tuberculosis of the tonsils.



# CHRONIC PROGRESSIVE OCCLUSION OF THE INFERIOR VENA CAVA AND THE RENAL AND PORTAL VEINS

WITH THE CLINICAL PICTURE OF THE NEPHROTIC SYNDROME  
REPORT OF A CASE, WITH A REVIEW  
OF THE LITERATURE

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The following case of progressive thrombosis of the inferior vena cava and the renal and portal veins is reported because (1) the condition is exceedingly rare, (2) the patient presented the clinical picture of the nephrotic syndrome and (3) pyelograms taken after intravenous injection of diodrast were suggestive of polycystic disease of the kidneys

## REPORT OF CASE

M L, 15 year old schoolboy, an American Jew, had a history of measles in 1927 and tonsillectomy in 1928. He entered the hospital on March 9, 1936, because of swelling of the abdomen and the lower extremities. The family history revealed that the boy's father had died of cerebral hemorrhage. The boy had been well until January 1935, when he began to complain of "sour stomach," the attacks being characterized by loss of appetite, nausea, vomiting and belching without pain. The first attack lasted two days. After a symptomless interval of two months there was a recurrence lasting three days. He then enjoyed good health until May 20, when he suffered an attack of nausea and vomiting accompanied by pain in the left costovertebral region and in the lower part of the back lasting three days. On May 31 the costovertebral pain recurred and radiated across the back and over the left side of the abdomen. It was associated with a slight headache, chilly sensations and frequency of urination. Because of the increased severity of the pain and the development of fever the patient was admitted to another hospital on June 1. Examination at that time revealed marked tenderness in the left costovertebral region. The blood pressure was 130 systolic and 90 diastolic. Twenty-eight examinations of the urine showed a specific gravity

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ranging from 1 002 to 1 017, with a slight to a very heavy trace of albumin in all specimens. The first specimen was alkaline, and its sediment showed an occasional white blood cell and 20 to 30 red blood cells per high power field. The majority of the remaining urinary sediments revealed no formed elements, several contained from 2 to 25 red blood cells, 1 to 10 white blood cells and many fine granular and hyaline casts per high power field. Gross hematuria was not observed. The red blood cell count on three occasions ranged between 4,510,000 and 5,000,000 per cubic millimeter, with a hemoglobin content of 87 to 95 per cent (Sahli). The white blood cell count on entry was 9,900 per cubic millimeter and one week later was 8,100. The nonprotein nitrogen content of the blood fluctuated between 24 and 32 mg per hundred cubic centimeters. The total protein content of the plasma was 6.2 and 5.5 Gm, respectively, on two occasions, and the albumin and the globulin content of the serum were 2.3 and 3.9 Gm per hundred cubic centimeters, respectively. The cholesterol content of the blood on one occasion was 164 mg per hundred cubic centimeters. The Pirquet reaction (1:1,000) was negative on two occasions. Excretion of phenolsulfonphthalein in one and two hours after intravenous injection of 1 cc of the dye was 80 and 7 per cent, respectively. An intravenous pyelogram faintly visualized both renal pelves and ureters, the pelves were small, and the calices were elongated and narrowed. The ureters showed no abnormality. A roentgenogram of the chest showed clear pulmonary fields. The temperature fell from 101 F to normal on the fourth day, and the costovertebral pain on the left rapidly disappeared. At no time was edema noted. The patient lost 13 pounds (5.9 Kg) in weight. The blood pressure fluctuated between 90 and 130 systolic and 60 and 86 diastolic. The basal metabolic rate was -25 per cent on one occasion. The patient was discharged to the care of his private physician on July 16 with a diagnosis of (?) lipoid nephrosis (without edema) and (?) chronic pyelonephritis.

The patient was well until August 8, when he noticed constant severe pain in the upper portion of the right lower abdominal quadrant, radiating to the right groin and at times to the right costovertebral angle and across to the midepigastrium. There was no nausea, vomiting, diarrhea, urinary symptoms, edema, chills or fever. After taking capsules prescribed by his private physician, the patient noticed redness of the urine the following day. Because of the persistence of the pain in the abdomen and the possibility of acute appendicitis or cholecystitis the patient was referred for the second time to the same hospital. Examination on entry revealed tenderness over McBurney's point and the right upper quadrant, with muscle spasm in both areas, especially marked in the latter. Slight costovertebral tenderness on the right was also noticed. There was no edema. Rectal examination gave negative results. The blood pressure was 110 systolic and 72 diastolic. Thirty-four examinations of the urine revealed a specific gravity ranging from 1.006 to 1.030. All the specimens contained from a trace to a very heavy trace of albumin, many showed up to 3 red blood cells, 1 to 20 white blood cells and 1 to 5 hyaline and granular casts per high power field. Doubly refractile bodies were not observed. The red blood cell count was 3,810,000 per cubic millimeter, the hemoglobin content fluctuated between 80 and 90 per cent (Sahli). The white blood cell count on entry was 9,600 per cubic millimeter, with a polymorphonuclear cell count of 65 per cent. Ten days later the white blood cell count was 16,500 per cubic millimeter. Six days afterward it fell to 11,800. Five determinations of the nonprotein nitrogen content of the blood gave values ranging from 19 to 29 mg per hundred cubic centimeters. The total protein content of the plasma on entry was 5.2 Gm, the albumin and the globulin content of the serum

being 15 and 37 Gm per hundred cubic centimeters, respectively. Three other examinations of the serum showed the total protein content to be 48, 49 and 44 Gm, the albumin content, 12, 11 and 14 Gm, and the globulin content, 36, 37 and 31 Gm per hundred cubic centimeters, respectively. The cholesterol content of the blood on entry was 125 mg per hundred cubic centimeters. The blood pressure fluctuated between 100 and 120 systolic and 60 and 76 diastolic. The basal metabolic rate on two occasions was  $-16$  and  $+2$  per cent, respectively.

On the thirteenth day after entry, because of continued pain in the right lower abdominal quadrant and the back and inability to extend the right leg without pain, the patient was transferred to the surgical service with a tentative diagnosis of appendicitis. On August 25 he was taken to the operating room because of the persistent pain in the right lower abdominal quadrant. Just before the operation slight edema and tenderness of the inner side of the right thigh were noted. The operation was postponed, the tenderness and pain subsided on the following day and the patient was transferred back to the medical service with a diagnosis of phlegmasia alba dolens. The right leg became swollen and tender and on August 27 the patient was unable to extend his right leg. Tenderness over the left Poupart ligament, tenderness and spasm in the left lower abdominal quadrant and edema of the upper portion of the right thigh were noted. A diagnosis of chronic nephritis and pelvic phlebitis was made at this time. On September 12 the patient had edema of the legs, scrotum and abdominal wall, with a suggestion of ascites. On September 19 the edema of the legs and scrotum showed considerable increase, but one week later it disappeared almost entirely. The temperature was normal from the day of entry until August 20, from August 21 to 25 it fluctuated between 98 and 100 F, from August 26 to 30 it was normal, from August 31 to September 2 it fluctuated between 98 and 99 F, and from September 3 to October 15 it was normal. Before the patient's discharge from the hospital the edema completely disappeared. Prominence of the veins of the abdominal wall was not noted. The patient was discharged to the care of his private physician on October 15, with a diagnosis of (?) chronic nephrosis and the (?) nephrotic stage of chronic nephritis and thrombophlebitis.

The patient did well until two months before admission to the Beth Israel Hospital, when he noticed recurrence of the edema of the legs. About two weeks before entry he became aware of distention of the abdomen. He was told by his private physician that there was fluid in the abdomen and was referred to the hospital. Examination on admission (March 9, 1936) revealed a pale, well developed boy in no acute distress. Ophthalmoscopic examination revealed myopia and temporal pallor of the disks. The heart was of normal size, with normal rhythm and no murmurs. The lungs showed rales at both bases, with diminished breath sounds and absence of tactile fremitus. The abdomen was distended and showed shifting dullness and a fluid wave. The superficial abdominal veins were prominent. There was a slight amount of pitting edema of both lower extremities. The blood pressure was 120 systolic and 95 diastolic. The deep reflexes were normal. Rectal examination gave negative results.

Twelve examinations of the urine revealed a specific gravity ranging as high as 1.038. All the specimens showed from a trace to a heavy trace of albumin, several contained occasional red blood cells, 1 to 5 white blood cells and 1 to 5 hyaline and granular casts per high power field. Doubly refractile bodies were not observed. The red blood cell count on entry was 4,940,000 per cubic millimeter and the hemoglobin value 96 per cent (Sahli). Ten days later these values were 4,400,000 per cubic millimeter and 85 per cent (Sahli), respectively. The white blood cell count was 8,150 per cubic millimeter on entry and 5,800

ten days later. The polymorphonuclear cell count was 65 per cent. One examination of the stool gave negative results. The nonprotein nitrogen content of the blood on two occasions was 37 and 23 mg per hundred cubic centimeters. The cholesterol content of the blood was 926 and 862 mg per hundred cubic centimeters. Determinations of the total protein content of the plasma gave values of 3.51, 3.61 and 3.52 Gm, the values for serum albumin being 1.58, 1.51 and 1.53 Gm and those for serum globulin being 1.93, 2.1 and 1.99 Gm per hundred cubic centimeters. The Kahn and Hinton reactions of the blood were negative. The basal metabolic rate was —19 per cent.

The patient was given a diet high in protein and low in fat and salt with restricted fluids. His blood pressure fluctuated about an average value of 120 systolic and 84 diastolic. The temperature was normal except on several occasions, when 99 was reached. The patient was free from symptoms except for occasional pain in the midhypogastrium, radiating to the back. His weight fluctuated about 145 pounds (65.8 Kg) without any change in the edema. Large doses of urea and later of thyroid did not increase the urinary output. On March 26, after nineteen days in the hospital, the patient was discharged to his private physician, with a diagnosis of chronic glomerular nephritis with edema (nephrotic syndrome). He was advised to take a low salt diet, with fluids restricted to 1,200 cc per twenty-four hours.

On April 20 the patient was readmitted to the Beth Israel Hospital. The interval history revealed that after discharge from the hospital he had remained in bed and the ascites had gradually disappeared in about three weeks. About one week before his second entry he awoke one morning with pain, stiffness and fulness in the right side of the neck. The pain and swelling became worse and were not relieved by alcohol rubs and hot poultices. Two days later the entire right upper extremity was swollen but not painful. The patient was referred to the hospital.

Examination revealed a slightly tender, movable, firm pea-sized mass over the right sternomastoid muscle, with a thickened cord extending downward from the lower border, its course corresponding to that of the external jugular vein. The right upper extremity was swollen, especially the upper portion, with only slight involvement of the hand, venous engorgement was not observed. The infraclavicular and supraclavicular regions were markedly tender. Red streaks along the right arm were not seen. There was no difference in temperature between the two arms. The lungs revealed dullness at both bases, with diminished breath sounds, probably due to the high diaphragm. The heart was not enlarged. The abdomen was distended, and the veins over it and the lower part of the chest were prominent. Shifting dullness and a fluid wave were elicited. The legs showed slight pitting edema. The blood pressure was 118 systolic and 98 diastolic. Thirty-three examinations of the urine revealed a specific gravity ranging from 1.008 to 1.036. All the specimens showed from a slight trace to a trace of albumin. Five specimens contained 1 to 5 red blood cells per high power field. Most of them contained 1 to 15 white blood cells and occasional hyaline and granular casts. Three specimens were loaded with granular and cellular casts. Doubly refractile bodies were seen on only one occasion, on which they were abundant. The red blood cell count varied between 4,600,000 and 5,500,000 per cubic millimeter. The hemoglobin content on several occasions was 85 per cent (Sahl). The white blood cell count on entry was 18,000 per cubic millimeter and fell to 9,900 three days later. Several white blood cell counts taken subsequently revealed variations between 5,000 and 8,000 per cubic millimeter. The polymorphonuclear cell count on entry was 79 per cent. Seventeen days

later it was 60 per cent. The blood smear on two occasions showed abundant platelets and slight achromia of the red blood cells. Two examinations of the stool gave negative results. Four determinations of the nonprotein nitrogen content of the blood showed the highest value to be 35 mg per hundred cubic centimeters. The sugar content was 74 mg per hundred cubic centimeters. The cholesterol content on entry was 431 mg per hundred cubic centimeters, ten and twenty-two days later, it was 520 and 594 mg respectively. The urea nitrogen content of the blood on two occasions was 13.1 and 10.4 mg per hundred cubic centimeters. On entry the values for the total protein, the albumin and the globulin content of the serum were 3.99, 1.93 and 2.06 Gm per hundred cubic centimeters, respectively. Ten days later these values were 4.12, 1.73 and 2.34 Gm, respectively. Thirty-two days after admission the value for serum albumin was 2.1 Gm and that for serum globulin was 1.79 Gm per hundred cubic centimeters. The basal metabolic rate on two occasions was —40 and —30 per cent, respectively. Roentgen examination of the kidneys showed the renal outlines to be large and regular in contour. Intravenous pyelograms showed the pelves incompletely filled. The calices were well outlined, and the cups were deep. The infundibula were somewhat elongated, "probably owing to polycystic kidneys." The ureters showed no deviation from the normal. There was good excretion of the dye through both kidneys within five minutes after the injection.

The patient was given a high protein, low salt diet, with fluids to 1,500 cc. The temperature, which on entry had been 102.2 F, fell to normal the next day and remained so. The pulse rate fell from 120 to 90 and several days later became normal. The blood pressure remained in the region of 110 systolic and 70 diastolic. The swelling and tenderness of the right side of the neck slowly subsided, as did the swelling of the right upper extremity. The superficial abdominal and the lower thoracic veins were more prominent. The weight on entry was 122½ pounds (55.3 Kg). There was a gradual increase in weight, 134 pounds (60.8 Kg) being recorded on the day of discharge. The daily urinary output varied between 1,000 and 1,500 cc. Urea, potassium nitrate and ammonium chloride were ineffective in increasing the volume of urine. On two occasions 2 cc of salyrgan given intravenously resulted in moderate diuresis. It was noted for the first time that there was evidence of obstruction of the portal vein. On the day of discharge to his private physician (May 31) the patient was up and about and was free from edema of the lower extremities. The abdomen, however, showed signs of fluid. The diagnosis on discharge was thrombophlebitis of the right external jugular vein, the nephrotic stage of chronic glomerular nephritis and (?) polycystic kidneys. The patient was advised to take a low salt, high caloric, high vitamin, high protein diet, with limitation of fluids to 1,500 cc per twenty-four hours.

After discharge from the hospital he followed the course prescribed, without any change in his condition.

From July 20 to September 22 he was studied at another hospital. During this period ascites, slight edema of the lower extremities and dilatation of the superficial veins of the upper part of the abdomen and the lower part of the thorax remained unchanged. The blood pressure fluctuated between 106 and 120 systolic and 66 and 80 diastolic. Seven examinations of the urine revealed a specific gravity ranging from 1.018 to 1.031. All the specimens showed from a trace to a heavy trace of albumin. The sediments showed occasional red blood cells, rare to numerous white blood cells and hyaline, granular and cellular casts. On one occasion a few doubly refractile bodies were seen. The red blood cell count varied between 4,830,000 and 5,800,000 per cubic millimeter. The

hemoglobin content fluctuated between 87 and 96 per cent. Three white blood cell counts gave respective values of 6,900, 7,000 and 7,950 per cubic millimeter. Eight determinations of the nonprotein nitrogen content of the blood showed values between 23 and 47 mg per hundred cubic centimeters. The urea nitrogen content of the blood on two occasions was 14 and 5.5 mg per hundred cubic centimeters. Nine determinations of the value for the total protein, the albumin and the globulin content of the serum showed the highest values to be 4, 1.21 and 3 Gm per hundred cubic centimeters, respectively. The cholesterol content of the blood fluctuated between 425 and 800 mg per hundred cubic centimeters. Numerous tests of the basal metabolism revealed values between  $-21$  and  $-30$  per cent. Roentgen examination of the abdomen showed the kidneys to be larger than normal.

The patient's weight on entry was  $132\frac{1}{2}$  pounds (60 Kg). There was a gradual increase in weight to  $142\frac{1}{4}$  pounds (64.5 Kg) shortly before his discharge. The daily output of urine varied between 215 and 990 cc. The patient was discharged unimproved to his private physician with recommendations for a high protein, low salt, low acid-ash diet. The diagnosis on discharge was thrombosis of the portal vein, thrombosis of the renal veins, nephrosis and migrating thrombophlebitis.

The patient was admitted for the third time to the Beth Israel Hospital, on Oct. 2, 1936, because of a severe chill thirty-six hours before, followed by fever and persistent nausea and vomiting. For the twenty-four hours preceding entry the patient suffered from profuse diarrhea. Three days previously the patient and his sister had eaten some meat, and immediately thereafter both complained of nausea, which persisted in the patient. The sister vomited two days and again one day before the patient's entry to the hospital, with complete disappearance of her symptoms. The patient's chill lasted one hour, after which the temperature rose to  $104.6^{\circ}\text{F}$ , gradually falling within the next twenty-four hours to  $99^{\circ}\text{F}$ . About six hours before his admission to the hospital it was still  $99^{\circ}\text{F}$ . Since the onset his breathing had been rapid, and during the few hours before entry he became irrational. The stools were profuse and watery, and he had three or four bowel movements every hour, without gross blood. He complained of pain in the lower portion of the abdomen and in the right groin. The costo-vertebral region on both sides was tender.

Examination revealed a comatose, dehydrated boy who breathed deeply, rapidly and irregularly. The heart was not enlarged, the cardiac rate was 140 beats per minute. The blood pressure was 78 systolic and 56 diastolic. The lungs revealed a few rales at both bases. The abdomen contained a considerable amount of fluid, the superficial abdominal and the lower thoracic veins were larger than on the previous entry. Tenderness was elicited throughout the abdomen. The edge of the liver was smooth and was felt 2 fingerbreadths below the right costal margin. Brawny edema of the upper part of each thigh was noted. The deep reflexes were equal and active bilaterally.

Examination of the urine revealed a specific gravity of 1.020 and a heavy trace of albumin. The sediment contained 18 to 25 white blood cells, 3 to 6 red blood cells and 1 to 4 granular and cellular casts per high power field. The red blood cell count was 4,450,000 per cubic millimeter, and the hemoglobin value was 80 per cent (Tallqvist). The white blood cell count was 8,500 per cubic millimeter, with a polymorphonuclear cell count of 90 per cent. Examination of the stool failed to reveal occult blood, and microscopic examination showed numerous white blood cells. The nonprotein nitrogen content of the blood was 45 mg per hundred cubic centimeters, the sugar content was 72 mg, and the

carbon dioxide-combining power was 327 volumes per cent. The Kahn and Hinton reactions of the blood were negative. Serum agglutination tests for typhoid bacilli and for paratyphoid bacilli A and B gave negative results.

Shortly after entry the patient lapsed into coma, from which he did not recover. He received intravenous infusions of 5 per cent dextrose and 1 per cent sodium bicarbonate in distilled water and physiologic solution of sodium chloride. The blood pressure rose temporarily to 100 systolic and 70 diastolic but soon fell to 60 systolic and 40 diastolic. The temperature varied between 104 and 106 F. The pulse rate was about 160, and the respiratory rate varied between 40 and 58. He died twenty hours after entry.

*Autopsy*—Autopsy was performed three hours after death. Only an abdominal incision was permitted. The peritoneal cavity contained cloudy, straw-colored,

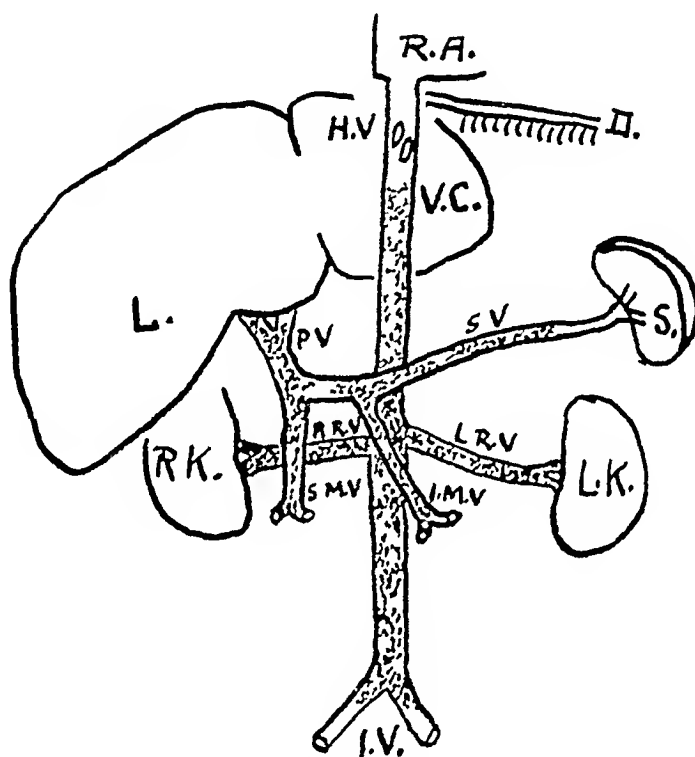


Fig 1—Diagram of the thrombosed vessels. *V.C.* indicates inferior vena cava, *P.V.*, portal vein, *S.V.*, splenic vein, *L.R.V.*, left renal vein, *R.R.V.*, right renal vein, *S.M.V.*, superior mesenteric vein, *I.M.V.*, inferior mesenteric vein, *H.V.*, hepatic veins, *I.V.*, iliac veins, *R.A.*, right auricle, *D.*, diaphragm, *L.*, liver, *S.*, spleen, *R.K.*, right kidney, and *L.K.*, left kidney.

thin fluid, a smear of which showed polymorphonuclear leukocytes, lymphocytes and pneumococci. The peritoneal surfaces were smooth, shiny and moist. The foramen of Winslow was closed by filmy adhesions, which were binding down the left lobe of the liver. All the retroperitoneal tissues were thickened, porky and edematous. The mesenteric lymph nodes were small. The pleural cavities contained no free fluid and the pericardial cavity no excess fluid.

Almost the entire inferior vena cava was completely occluded and replaced by a solid cord, about 1 to 1.5 cm in diameter. The occlusion began at the junction of the common iliac veins (fig 1) and extended throughout the course

of the inferior vena cava to a point about 2 cm distal to the entrance of the hepatic veins. Cross section of this solid cord revealed a pale, gray-brown tissue with no lumen. External pressure on this solid cord resulted in the exudation of blood from several small points on the cut surface. When these points were probed they led to a few longitudinal, tortuous channels with narrowed lumens. Both renal veins were similarly occluded from their junction with the inferior vena cava to the hilus of each kidney. The branches of the renal veins were patent, and there were no gross intrarenal thromboses.

A similar type of occlusion was present in the portal venous system, starting at the hilus of the liver but not involving the intrahepatic branches of the portal vein. The portal vein and its tributaries, the splenic vein and the inferior and superior mesenteric veins, were likewise solid cords. The distal portion of the splenic vein near the hilus of the spleen was patent, as were the distal

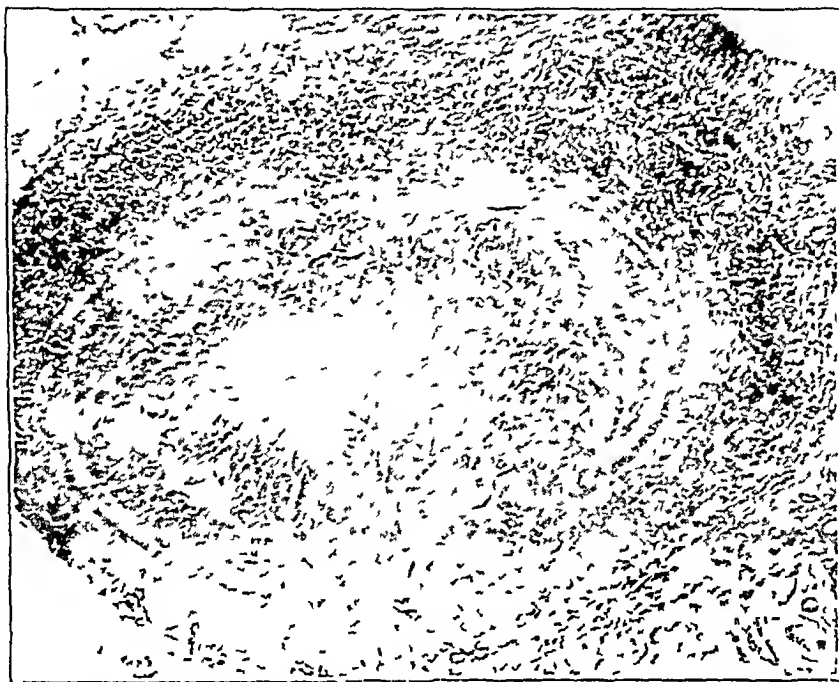


Fig 2—Transverse section ( $\times 30$ ) of the inferior vena cava, showing complete thrombosis with recanalization

branches of both mesenteric veins. The azygos and the superficial epigastric veins were dilated. The restricted incision precluded proper study of the system of the superior vena cava.

Microscopically a similar picture was observed in the inferior vena cava, the renal veins, the portal vein and its branches and also the peritracheal veins (figs 2 to 6). The lumens of all these vessels were obliterated in all regions by thrombi of various ages. For the most part these lumens were replaced by a network of tortuous, endothelium-lined, sinusoid-like channels, the total cross section of which was much smaller than the original channel. The original wall, with its muscular media, was still generally recognizable. No intima was present. It was replaced throughout by a rather loose fibrous tissue continuous with that in the broad trabeculae separating the sinusoidal channels. Only occasionally in these trabeculae were there small collections of hemosiderin-laden monocytes. More rarely even a scattering of lymphocytes was seen in this





Fig 3—Longitudinal section ( $\times 20$ ) of the inferior cava, showing the recanalized thrombus with fresh thrombi in many of the smaller venous channels



Fig 4—Longitudinal section ( $\times 30$ ) through the portal vein, showing the recanalized thrombus

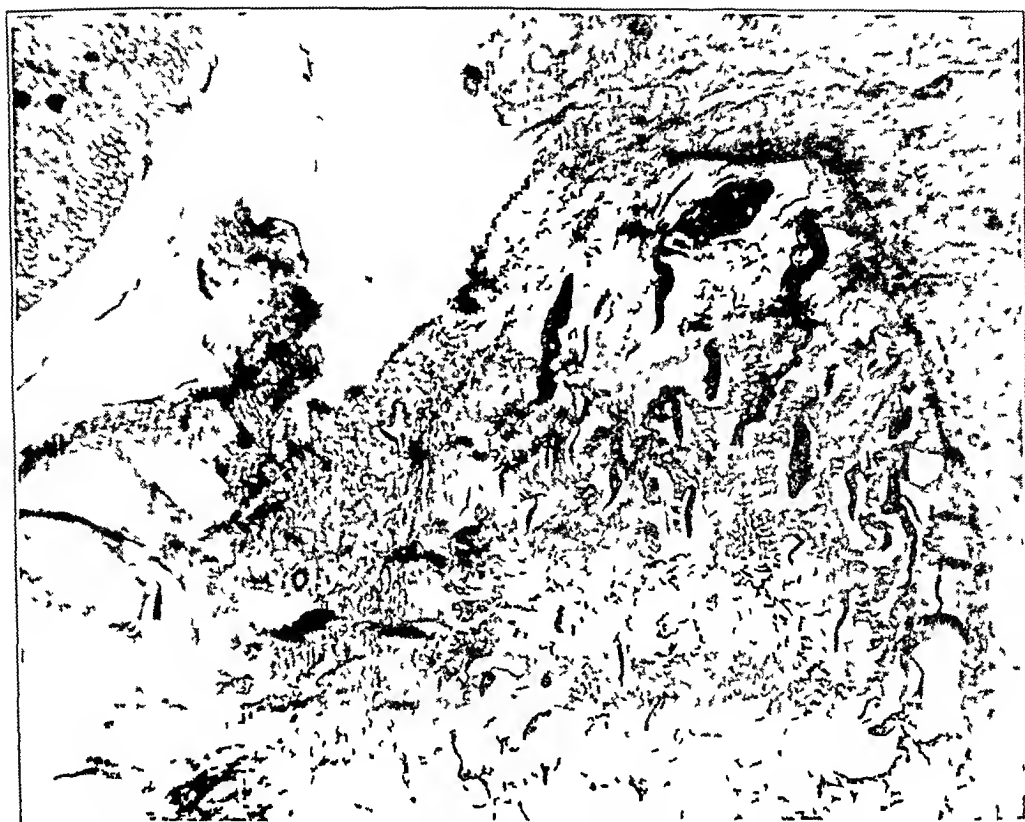


Fig 5—Section ( $\times 30$ ) through the renal vein, showing the recanalized thrombus and numerous smaller venous channels containing fresh thrombi



Fig 6—Section ( $\times 30$ ) of the trachea, showing the recanalized thrombosed veins, some of which contain fresh thrombi

region. An occasional collection of fat-laden monocytes was also present, especially in the portal vein. Besides this picture of an old healed process there was evidence that the mechanism leading to occlusion was still active.

In all the sections from the occluded veins there were small fresh thrombi forming in some of the sinusoidal spaces. Rarely did such a thrombus fill the space. Usually it was attached to the wall at only one point. It consisted largely of fused platelet strands, fibrin fibrils or fused fibrin or a mixture of these ingredients. Entangled blood cells were uncommon. Invasion and organization by fibroblasts growing out from the point of attachment comprised the usual picture. Often a knot of fused hyaline material was present in the midst of a projection into a sinusoid, obviously a small, almost organized, recently formed thrombus.

The heart weighed 240 Gm and showed no abnormality of the myocardium or endocardium. A few petechial hemorrhages were present in the epicardium. The coronary arteries showed no disease. The abdominal aorta was only 4 cm in diameter, and there were several scattered arteriosclerotic plaques.

The kidneys were large, each weighing 360 Gm. Their capsules were not thickened and were easily stripped, revealing smooth, shiny, bluish red, congested surfaces. The cut surfaces were smooth and showed distinct markings throughout. The cortex was everywhere sharply differentiated from the medulla, had a thickness of 0.8 cm and was uniformly bluish red with an occasional yellowish area, especially at the upper poles. The medulla of the kidneys was pale red with a characteristic yellowish tinge. The amount of pelvic fat was not increased. The pelves were not dilated, and the calices revealed smooth and shiny mucosa.

Microscopically the glomeruli were of normal size, without any degeneration or proliferation of the epithelium or endothelium (fig 7). The capillary tufts were unobstructed and did not contain any polymorphonuclear leukocytes. Droplets of fat in the glomeruli were not demonstrated with the scarlet red stain. The tubular epithelium showed slight cloudy swelling (fig 8). Many tubules contained granular debris without any cellular elements. The scarlet red stain revealed a rare droplet of fat in the tubular epithelium. Doubly refractile bodies were not seen. There was no structural change in the arterioles and arteries. Intrarenal venous thrombosis was observed in one spot only. The interstitial tissue was edematous and contained an occasional focus of round cells. Sections stained by the McGregor technique<sup>1</sup> revealed no thickening of Bowman's capsule or of the glomerular basement membrane (fig 9). No intracapillary fibrin or hyaline fibers were seen.

The liver weighed 1,960 Gm and was grossly normal except for congestion. Microscopic examination revealed cloudy swelling, marked congestion and dilatation of the sinusoids and dilatation of the central veins without necrosis of the hepatic cells. There was no suggestion of cirrhosis.

The spleen weighed 370 Gm and was not remarkable on gross or microscopic examination. Culture gave negative results.

The rest of the viscera were normal except for slight diffuse fibrosis of the alveolar walls of the lungs and congestion and edema of the intestines.

*Summary of the Case*—A 15 year old schoolboy, an American Jew, began to suffer from attacks of nausea, vomiting and anorexia twenty-two months before

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<sup>1</sup> McGregor, L. The Finer Histology of the Normal Glomerulus, *Am J Path* 6 545, 1929, The Cytological Changes Occurring in the Glomerulus of Clinical Glomerulonephritis, *ibid* 6 559, 1929.

his first admission to the hospital. Five months later he had an attack of costo-vertebral pain on the left, which was diagnosed as due to pyelonephritis and nephrosis. One month later he had pain in the right lower abdominal quadrant, radiating to the right groin, to the costovertebral region on the right and across to the midepigastrium, accompanied by spasm and tenderness in the right abdominal quadrants. There were edema and tenderness of the inner side of the right thigh, followed by edema of both legs, the scrotum and the abdominal wall and tenderness and spasm over the left lower abdominal quadrant. The edema disappeared several weeks later. Nine months before his admission to the hospital, edema of the legs occurred, followed by swelling of the abdomen. Three months later he had thrombophlebitis of the right external jugular vein and questionable similar involvement of the right subclavian vein. Prominent veins of the

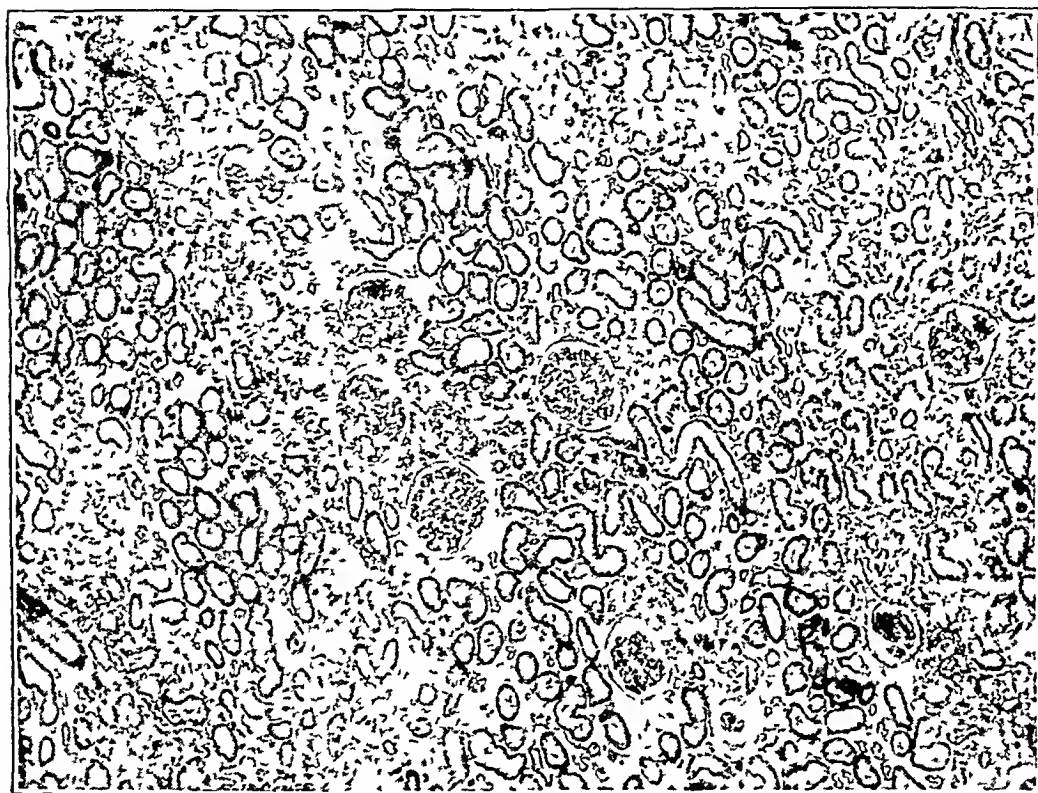


Fig 7—Section ( $\times 50$ ) of the kidney, showing interstitial edema

abdominal wall and the lower part of the thoracic wall appeared. Three days before entry the boy had chills, fever, nausea and vomiting, followed by severe diarrhea, coma and death. Physical examination gave negative results except for distention of the abdomen with fluid, prominent superficial veins of the abdomen and the lower anterior portion of the chest and slight pitting edema of the legs. The blood pressure was normal throughout the illness. Laboratory examinations revealed no anemia or impairment of renal function, there were massive albuminuria, a few red and white blood cells, casts and doubly refractile bodies in the urinary sediment, hypercholesteremia and hypoproteinemia, with reversal of the albumin-globulin ratio (table).

Postmortem examination revealed pneumococcal peritonitis, enlarged and swollen kidneys and old recanalized and fresh fibrin thrombi in the inferior vena

Date	Urinalysis*							Blood Chemistry						
	Num ber of Ex amina tions	Specific Gravity	Albu min†	Formed Elements After Centrifuga tion (Per High Power Field)				Total Pro tein, Gm per 100 Cc	Serum Albu min, Gm per 100 Cc	Serum Glob ulin, Gm per 100 Cc	Choles terol, Mg per 100 Cc	Urea Nitro gen, Mg per 100 Cc	Non protein Nitro gen, Mg per 100 Cc	Sugar, Mg per 100 Cc
				Casts	White Blood Cells	Red Blood Cells	Doubly Refrac tile Bodies							
1935														
January														
March														
May 20														
May 31														
June 1 to July 16	28	1 002 to 1 017	S T to V H T	0 to many hyaline and coarse brown granular	0 10	0 25	0	6 20 5 50	2 30	3 90	164		30 27 27 32 24 29 32 29	
Aug 12 to Oct 15	34	1 006 to 1 030	T to V H T	1 to 5 hyaline and granular	1 20	0 3	0	5 20 4 80 4 90 4 40	1 50 1 20 1 10 1 40	3 70 3 60 3 70 3 10	125		29 27 25 27 19	
1936														
March 9 to March 28	12	1 020 to 1 038	T to H T	0 to 1 hyaline and 0 to 5 granular	0 5	0 1	0	3 51 3 61 3 52	1 58 1 51 1 58	1 93 2 10 1 99	926		37 23	
April 21 to May 31	29	1 008 to 1 036	S T to T	0 to 1 hyaline, 0 to loaded granular and cellular	0 25	0 5	—	3 99 4 12	1 93 1 78 2 10	2 06 2 34 1 79	431 520 446 594	13 10	31 35 31 32	74
July 20 to Sept 22	7	1 018 to 1 031	0 5 to 2 0%	Rare to numerous hyaline, granular and cellular	Rare to numer ous	Rare	+	2 70 2 40 2 10 3 35 3 80 4 00 3 49 3 65 2 63	0 81 0 60 0 75 0 78 1 00 1 00 1 21 1 06 1 13	1 89 1 80 1 35 2 57 2 80 3 00 2 28 2 59 1 50	690 516 445 425 571 640 800 769 800	14 5 5	27 3 27 28 1 42 23 47 28 6 29 1	
Oct 2 to Oct 3	1	1 020	H T	1 to 4 granular and cellular	18 25	3 6					327		45	72

† Heller's ring test (read after 1 minute) S P T indicates slightest possible trace, V S T, very slight trace.  
 \* Benedict's qualitative test for sugar gave a negative reaction in all specimens of urine

and Laboratory Findings

Hematologic Picture			Blood Pressure, Mm Hg		Basal Meta- bolic Rate, per Cent	Symptoms	Probable Venous Lesions	Edema	Collateral Circulation
Hemo- globin, per Cent	Red Blood Cells, Millions	White Blood Cells	Sys- tole	Diastolic					
						"Sour stomach"			
						"Sour stomach"			
						Nausea and vomit- ing, pain in costo- vertebral region and back (3 days)			
						Costovertebral pain on left, fre- quency of urination	Thrombosis of left renal vein		
90	4.51	9,900	90-130	60-86	-25	Subsidence of pain and urinary symptoms		0	
95	5.00	8,100							
92	4.55								
80		9,600							
85	3.81	16,500	100 to	60-70	-16	Pain in right lower abdominal quad- rant radiating to right costovertebral region and mid epigastrium, costo- vertebral tender- ness on right	Thrombosis of right renal vein, pelvic phlebitis, thrombosis of inferior vena cava and portal vein	Thighs, legs, scrotum and abdominal wall	
90		11,800	120		+ 2				
90	4.94	8,150							
96	4.95		120	84	-19	Recurrent edema of legs, ascites, occasional pain in hypogastrium radiating to back		Legs, ascites	Prominent veins in abdominal wall
85	4.44	5,800							
85	5.00	18,000							
85	4.65	9,900	110	70	-40	Pain and fullness in right side of neck, swelling of right arm	Phlebitis of right external jugular and (?) right subclavian veins	Legs, ascites	Prominent veins in abdominal wall and lower ante- rior part of thorax
70	4.60	10,700			-30				
75	4.90	5,000							
85	5.50	9,800							
		8,500							
		8,000							
96	5.80				-21				
87	4.86				-24				
87	4.96	6,900			-25			Thighs and legs, ascites	Dilatation of superficial veins of up- per portion of abdomen and lower portion of anterior thorax
88	4.88		106	66	-28				
89	5.04	7,000	to	to	-27				
92	5.57		120	80	-29				
88	4.96	7,950			-30				
94	5.21				-29.5				
					-26.4				
					-26				
80	4.45	8,500	70-100	40-70		Gastroenteritis		Thighs, ascites	Prominent veins in abdominal wall and lower ante- rior portion of thorax

ST, slight trace T, trace, HT, heavy trace, VHT, very heavy trace

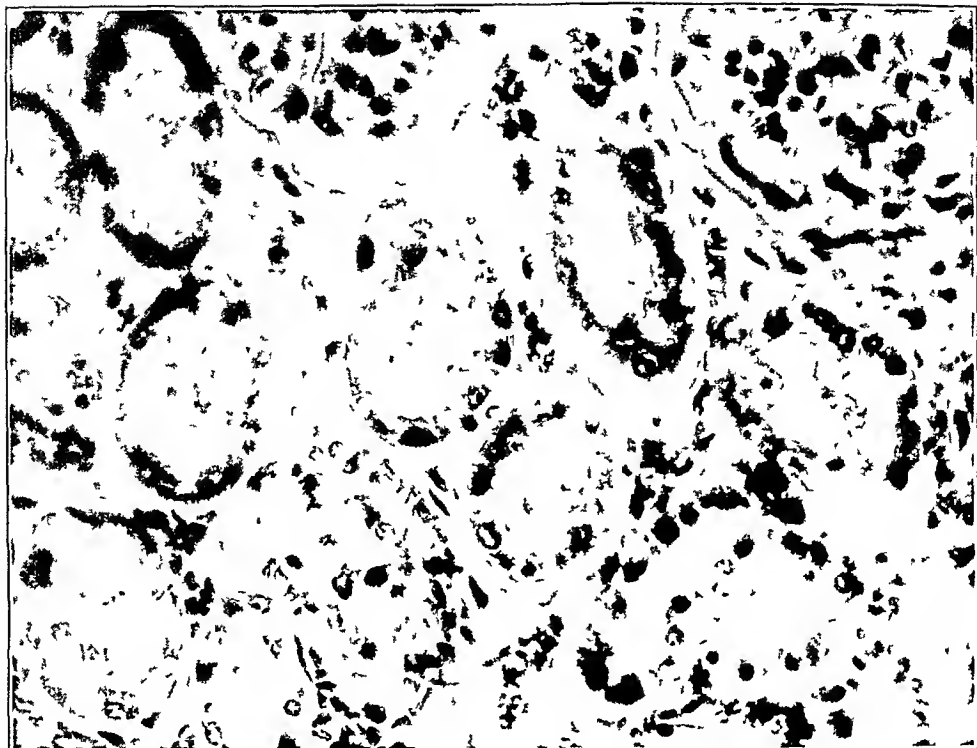


Fig 8—Section ( $\times 200$ ) of the kidney, showing slight cloudy swelling of the tubular epithelium. The interstitial tissue is edematous.

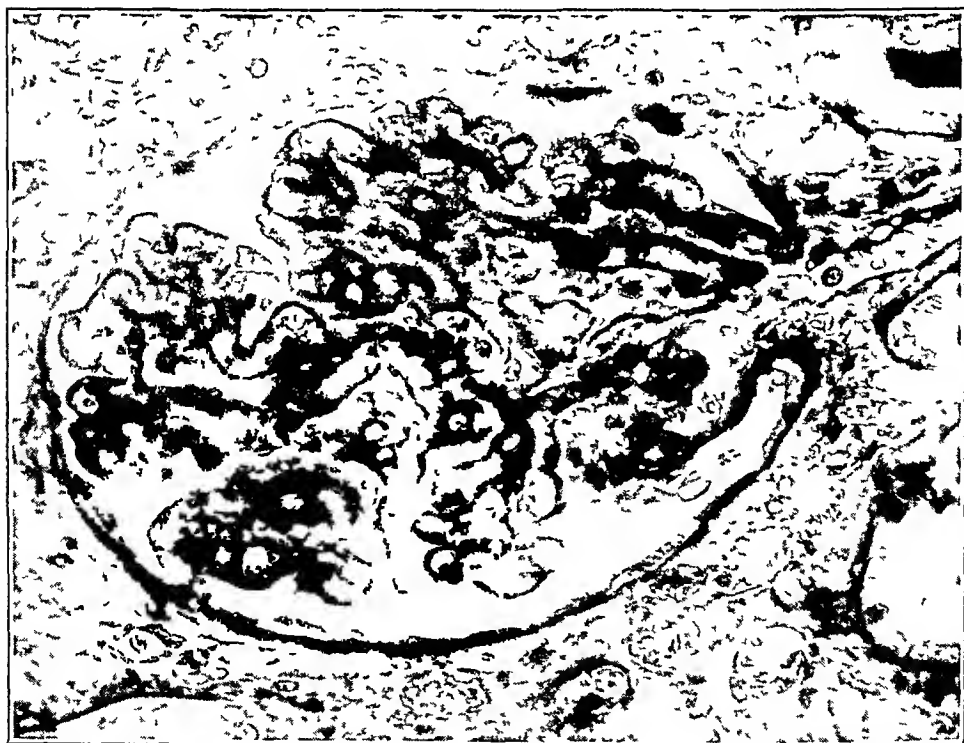


Fig 9—Section ( $\times 400$ ) of the kidney, stained by the McGregor technic, showing a normal glomerulus.

cava, the peritracheal, portal, splenic and renal veins and the proximal portions of the mesenteric veins. Microscopic examination of the kidneys revealed no abnormality of the glomerular epithelium, endothelium or basement membrane. The tubules showed slight cloudy swelling and no doubly refractile bodies. The interstitial tissue was edematous. The heart, lungs, liver, spleen and pancreas were normal on gross and microscopic examination.

#### REVIEW OF LITERATURE

The literature dealing with venous thrombosis is extensive. The important features applicable to this case are herewith presented.

*Thrombosis of the Portal Vein*—The clinical picture and pathologic anatomy of this condition have recently been thoroughly reviewed by Simonds<sup>2</sup> and need not be discussed at this point except to state that the manifestations of thrombosis of the portal vein in our case were ascites, collateral circulation and abdominal pain. Hematemesis and a palpable spleen were not present. Simonds found that the most common causes of death were hemorrhage and intestinal infarction. Our patient died of pneumococcal peritonitis. Cases of thrombosis of the portal vein associated with other venous thromboses or with nephrosis were not mentioned by Simonds<sup>2</sup> or by Weir and Beaver<sup>3</sup>.

*Thrombosis of the Inferior Vena Cava*—The clinical picture and pathologic anatomy of this condition have been adequately described by many observers.<sup>4</sup> The two important signs of thrombosis of the inferior vena cava are edema of the lower extremities and the development of a characteristic collateral circulation. It is not well recognized that slow occlusion is compatible with a long life. The presence or absence of albuminuria helps to determine the location of the thrombosis, if present, it indicates thrombosis above the entrance of the renal veins, and if absent, it indicates thrombosis below the entrance of the renal veins. During the course of his illness our patient had edema of the lower extremities but the collateral circulation was typical of thrombosis of the portal vein.

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2 Simonds, J. P. Chronic Occlusion of the Portal Vein, Arch Surg **33**: 397 (Sept) 1936.

3 Weir, J. F., and Beaver, D. C. Diseases of the Portal Vein. A Review of One Hundred and Twenty-Seven Cases, Am J Digest Dis & Nutrition **1** 498, 1934.

4 (a) Blumer, G. Thrombosis of the Inferior Vena Cava, in Osler, W. Modern Medicine, Philadelphia, Lea & Febiger, 1907, vol 4, p 529. (b) Heilmeyer, L., and Lippross, O. Ueber doppelseitige Nierenvenenthrombose bei Erwachsenen, Deutsches Arch f klin Med **179** 80, 1936. (c) Osler, W. Case of Obliteration of Inferior Vena Cava with Great Stenosis of the Orifices of the Hepatic Veins, J Anat & Physiol **13** 291, 1878-1879.



*Thrombosis of the Renal Veins*—Acute primary thrombosis of the renal veins is rare in adults but more common in infants<sup>5</sup> The clinical features are albuminuria, bloody urine, oliguria, palpable kidneys which grow larger under observation, uremia and death Hemorrhagic infarction, with extensive thrombosis of the renal veins extending into their smaller radicles, is usually present In some cases the infarction is attributed to multiple capillary thromboses and less extensive thrombosis of the renal veins

Chronic glomerular nephritis, amyloid disease, pyelonephritis or eclampsia may present an acute terminal picture of uremia owing to the presence of multiple thrombi in the main and medium-sized branches of the renal veins, which results in the picture of infarction and necrosis of the kidneys<sup>6</sup>

Thrombosis of the renal veins may develop from the intravenous extension of thrombophlebitis of the inferior vena cava or phlebitis of the leg or the pelvic organs<sup>7</sup> If the involvement is unilateral the condition may be amenable to surgical intervention<sup>8</sup>

Cases of thrombosis of the renal veins caused by extension from a renal or an adrenal tumor or compression by a retroperitoneal neoplasm or an aneurysm have been reported<sup>9</sup>

The experimental production of acute (bilateral and unilateral) thrombosis of the renal veins has been carried out by many investigators<sup>10</sup>

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5 Welch, W H Thrombosis, in Allbutt, T C System of Medicine, New York, Macmillan & Company, 1899, vol 6, p 170 Aschner, P W Thrombosis and Thrombophlebitis of the Renal Veins, J Urol **17** 309, 1927 Oppenheim, F Ueber den hamorrhagischen Niereninfarkt der Sauglinge Ein anatomischer Beitrag zu dem Kapitel der toxischen Capillarwandschädigung, Ztschr f Kinderh **26** 192, 1920

6 Petremand, S Beitrag zur Kenntnis der Nierenvenenthrombose bei Sauglingen, Klin Wchnschr **2** 2244, 1923 Herzog, G Ueber hyaline Thrombose der kleinen Nierengefasse und einen Fall von Thrombose der Nierenvene, Beitr z path Anat u z allg Path **56** 175, 1913 Neu, J Ueber doppelzeitigen Nierenvenen Thrombose, Klin Wchnschr **1** 2001, 1922 Opsahl, R Pathology of Amyloid Kidney in Connection with Four Cases, Norsk mag f lægevidensk **97** 1028, 1936 Blumer<sup>4a</sup> Heilmeyer and Lippross<sup>4b</sup>

7 Reese, H Zur Symptomatologie der Nierenvenen Thrombose, Deutsches Arch f klin Med **78** 588, 1903

8 Ehrstrom, R Die klinik der Niereninfarkte und der Nierenvenenthrombose, Acta med Scandinav **83** 458, 1934 Marion, G Necrose du rein droit par thrombose de la veine renale nephrectomie, guerison, J d'urol **15** 455, 1923

9 Hyman, A Clinical and Surgical Aspects of Renal Neoplasms, Surg, Gynec & Obst **41** 308, 1925

10 (a) Harrington, S W The Effect on the Kidney of Various Surgical Procedures on the Blood Supply, Capsule and on the Ureters, Arch Surg **2** 547 (May) 1921 (b) Rowntree, L G, Fitz, R, and Geraghty, J T The Effects of Experimental Chronic Passive Congestion on Renal Function, Arch Int Med **11** 121 (Feb) 1913

The clinical picture and pathologic anatomy of chronic thrombosis of the renal veins are not well known. Acute unilateral thrombosis of the renal vein may progress to a chronic stage after the initial hematuria and enlargement and tenderness of the kidney subside. Albuminuria may persist for months.<sup>7</sup> Gradual and progressive to complete obstruction of the renal vein, as produced by Rowntree<sup>10b</sup> in unilaterally nephrectomized dogs, resulted in albuminuria, normal renal function and the development of a collateral circulation involving the capsular, lumbar, ovarian and adrenal veins. Histologic studies of these kidneys were not reported. From the sequence of the symptoms in our case, thrombosis of the right renal vein presumably developed about ten weeks after a similar process had occurred in the left renal vein. The interval probably permitted an adequate collateral venous circulation from the left kidney to develop, so that acute renal failure did not follow the later occlusion of the right renal vein.

*Thrombosis of the Inferior Vena Cava and the Portal and Renal Veins*—Weber<sup>11</sup> and Shattock<sup>12</sup> reported cases of acute and chronic thrombosis of the inferior vena cava and the renal veins. Shattock's report revealed the unusual history of a 24 year old medical student who had severe pain in the lumbar portion of the spine after running a race. Edema of the legs and the lower part of the trunk supervened and was followed by progressive enlargement of the superficial veins of the abdomen. Albuminuria appeared at once and persisted throughout life. Death occurred twenty-five years later, the patient having carried on an active obstetric practice. Postmortem examination revealed the inferior vena cava to be converted into a flat, impervious ribbon extending from the point of entry of the hepatic veins downward below the renal veins. The latter were closed at their entrance to the inferior vena cava. The return of blood from the kidneys probably took place through the veins of the renal capsules, the lumbar veins and the azygos veins. The portal vein was not described. Microscopic studies were not made.

Careful search of the literature revealed only 1 reported case of thrombosis of the inferior vena cava and the portal vein.<sup>13</sup> The patient at the age of 34 had diffuse abdominal pain, most severe in the left hypochondrium, followed by fever, vomiting, anuria and transitory

11 Weber, F. P. Thrombosis of Inferior Vena Cava and Both Renal Veins, *Internat Clin* **3** 132, 1921, Thrombosis of Inferior Vena Cava and Both Renal Veins, *Proc Roy Soc Med (Sect Med)* **14** 9, 1921.

12 Shattock, S. G. Occlusion of the Inferior Vena Cava as a Result of Internal Trauma, *Proc Roy Soc Med (Path Sect)* **6** 126, 1913.

13 Lutembacher, R. Thrombo-phlebite de la veine cave inferieure et de la veine porte, *Presse med* **43** 1175, 1935.

albuminuria. Edema and ascites supervened and slowly disappeared over a period of fifteen to eighteen months as the collateral circulation developed. The author's excellent photographs show the extensive dilatation of the superficial veins of the groin, abdomen, and thorax. During the remaining fifteen months of his life the patient suffered from several attacks of abdominal pain. The cause of death was said to be hepatorenal insufficiency. Postmortem examination revealed old thrombosis of the inferior vena cava, extending from the bifurcation to the entrance of the hepatic veins, and more recent thrombosis of the portal vein. The renal veins were permeable. An adherent thrombus in the right renal vein extended into the inferior vena cava. The kidneys were large and showed on microscopic examination diffuse and complete degeneration of the tubular epithelium. It was felt that the tubular degeneration developed shortly before death. The liver was of normal size, its surface was nodular. Cut sections had an appearance typical of Laennec's cirrhosis. Microscopic examination revealed marked portal cirrhosis. The weight of the spleen was not given, but the organ measured 14 by 10 cm.

The case is unusual because of the spontaneous absorption of the edema and ascites brought about by the collateral circulation and the adequate renal function due to the permeability of the renal, lumbar and azygos veins.

*Thrombophlebitis Migrans*—The clinical picture and pathologic anatomy of this rare condition have been recently reviewed by Stern.<sup>14</sup> Thrombophlebitis migrans is characterized by phlebitis and often by thromboses involving long or short segments of deep or superficial veins. The migration from vein to vein and the subsidence of the process in one location and its appearance in another are distinctive features of this condition. Any organ may be affected, so that the patient may recover in several weeks or may die from the effects of the thrombotic lesions. Unless one of the superficial veins is involved at some time during the illness it is difficult to make a diagnosis of thrombophlebitis migrans. Arterial phenomena, which are outstanding features in Buerger's disease,<sup>15</sup> do not constitute a part of this entity. Of the 40 patients reported on in the literature, as reviewed by Stern, none showed thrombosis of the inferior vena cava and the portal and renal veins or presented the nephrotic syndrome clinically.

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14 Stern, N. S. Thrombophlebitis Migrans, *South M J* 27:849, 1934.

15 Buerger, L. The Circulatory Disturbances of the Extremities, Philadelphia, W. B. Saunders Company, 1924.

Progressive thrombosis of the veins, as described by Karsner<sup>16</sup> is probably the same entity as thrombophlebitis migrans. In his book entitled "Human Pathology" Karsner stated

Chronic phlebitis may constitute a part of that rare disease sometimes spoken of as progressive thrombosis of the veins. Trauma or some unknown condition may establish thrombosis in any vein of the body. Subsequently, other veins become involved, usually not by direct extension, until a number of chronic thrombi may be established in various situations.

Karsner observed 1 patient clinically, the illness beginning at the age of 30 and progressing over a period of more than twenty years. It was characterized by recurrent phlebitis of the superficial veins of the lower extremities. Visceral involvement was not noted.<sup>17</sup>

*Collateral Circulation*—The superficial collateral circulation in our case was characteristic of that associated with thrombosis of the portal vein, i. e., the superficial veins on the surface of the abdomen were near the median line of the lower part of the thorax and over the anterior portion of the abdominal wall between the xiphoid process and the symphysis pubis, with slight prominence around the umbilicus. The prominent superficial veins in the iliac and inguinal regions and along the lateral aspect of the lower part of the abdomen and the thorax observed in cases of obstruction of the inferior vena cava were not present.

*Roentgenographic Appearance of Kidneys in Chronic Thrombosis of the Renal Veins*—Pyelographic examination in our case revealed good excretion and concentration of the diodrast within five minutes after injection. Elongation and pressure defects of the calices and pelvis were noted (fig. 10). The kidneys were enlarged and were regular in contour. Over a period of almost a year further increase in the size of the kidneys was observed by measurement of the distance between the upper and the lower pole of each kidney.

	Right Kidney	Left Kidney
6/25/35	14.2 cm	13.6 cm
5/13/36	15.5 cm	15.1 cm

The deformity of the calices and pelvis resembled that caused by polycystic disease of the kidneys.<sup>18</sup> In our case, however, only edema of the interstitial tissue was present to explain the roentgenologic changes.

*Nephrotic Syndrome*—Albuminuria, cholesterolemia, slight hematuria, edema, hypoproteinemia, reversal of the albumin-globulin ratio,

16 Karsner, H. T. Human Pathology, Philadelphia, J. B. Lippincott Company, 1926, p. 475.

17 Karsner, H. T. Personal communication to the authors.

18 Macalpine, J. B. Cystoscopy and Urography, Baltimore, William Wood & Company, 1936, p. 414.

hypercholesterolemia and absence of hypertension and of impaired renal function are regarded as criteria of the nephrotic syndrome<sup>19</sup> The present case closely fulfils these clinical criteria, although none of the usual causes of the nephrotic syndrome, i. e., glomerular nephritis, amyloid disease or lipid nephrosis, was present There was no hepatic disease to explain the hypoproteinemia and the reversal of the albumin-globulin ratio

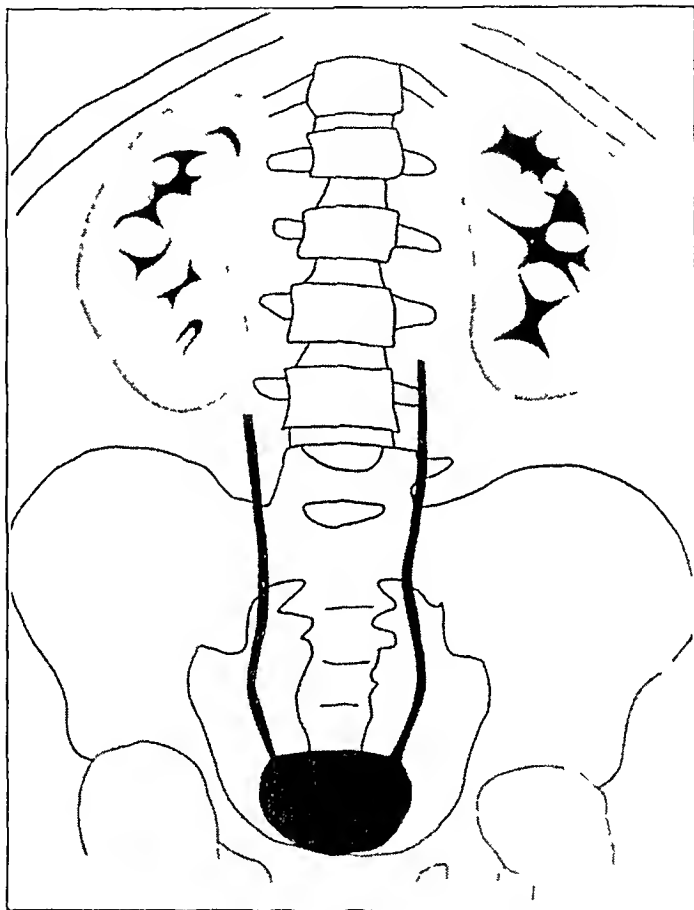


Fig 10—Schematic diagram of the pyelograms, showing pressure defects in the calices and pelves suggestive of polycystic disease

Throughout the last fifteen months of the patient's illness all the cardinal signs of the nephrotic syndrome were repeatedly found with the exception of hypercholesterolemia and the presence of doubly refractile bodies in the urine However, the former was observed consistently during the last seven months Doubly refractile bodies in the urine were observed on only two occasions, five and three months, respectively, before death

19 Leiter, L Nephrosis, *Medicine* 10 135, 1931

If the chronic thrombosis of the renal veins was the sole background for the nephrotic syndrome, as seems likely, this case is unique. No other case of chronic thrombosis of the portal or renal veins with the nephrotic syndrome or of the nephrotic syndrome with chronic thrombosis of the renal veins has been found after careful search of the literature. The nearest approach is in cases of edema due to active glomerular nephritis, with acute thrombosis of the renal veins occurring terminally. Such cases differ from cases of the nephrotic syndrome because of the presence of normal levels of protein in the plasma<sup>1b</sup> and the rapid development of uremia.

#### SUMMARY

A case of chronic progressive occlusion of the inferior vena cava and the renal and portal veins, with the clinical picture of the nephrotic syndrome, in which death was due to pneumococcal peritonitis is reported. Pyelograms were suggestive of polycystic disease of the kidneys. The kidneys, however, showed only slight cloudy swelling of the tubules and edema of the interstitial tissue, with no abnormality of the glomeruli.

Drs J B Manary and S J Thannhauser furnished data on the patient's condition during hospitalization elsewhere.

# TENSE PNEUMOTHORAX

TREATMENT OF CHRONIC AND RECURRENT FORMS BY  
INDUCTION OF CHEMICAL PLEURITIS

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Tense pneumothorax results when the communication between the lung and the pleura acts as a one way valve. Air can enter the pleural cavity during inspiration, but its escape is prevented during expiration, so that the pneumothorax tends to increase in size and tension. As the resulting dyspnea increases, the patient's inspiratory efforts become more vigorous, more air is pumped into the pleural cavity, and the condition is made more acute. This form of pneumothorax is not common, but it is important because of the distressing symptoms it may produce. Although it usually occurs as a complication of active pulmonary disease, there are instances in which there is little or no clinical evidence of a pathologic process in the lung and in which the etiology is not clear cases of so-called idiopathic tense pneumothorax.

The majority of patients with valvular, or tense, pneumothorax get well under conservative management. After a while, so much air is aspirated into the pleural cavity that the intrapleural pressure is raised sufficiently to keep the valvelike tear in the lung closed during both phases of respiration. If the patient can then be kept quiet enough to avoid unusual respiratory effort, the opening in the lung will tend to heal. Air acts as an irritant and produces enough inflammatory reaction about the injured part of the lung to result in sealing of the defect. Once this occurs, the pneumothorax will be absorbed and the lung will reexpand.

There is, however, a certain group of cases in which this condition may persist for months or even years. The patients remain chronic invalids because of the respiratory and cardiac embarrassment which they may suffer on little exertion.

Once a chronic state has become established, a cure will not occur unless a more vigorous inflammatory pleural reaction supervenes and brings about the sealing of the chronic, partially epithelized pleuropul-

monary communication. In this connection, it has been noted that the patients who for one reason or another contract active pleuritis with effusion recover soon afterward. This observation suggested the idea of attempting the induction of chemical pleuritis in cases of chronic and recurrent tense pneumothorax which showed no tendency to spontaneous recovery.

This idea first occurred to Spengler<sup>1</sup> in 1901. In 1906 he<sup>2</sup> suggested the use of a 0.5 per cent solution of silver nitrate for the production of the chemical pleuritis. In 1919 he<sup>3</sup> advised the use of a 30 per cent solution of dextrose for the same purpose. It was not until 1923<sup>4</sup> that he reported his first clinical case. He used 30 cc of a 30 per cent solution of dextrose in repeated doses and obtained a cure within four months. In his report he suggested that it would be desirable to use either larger amounts of the 30 per cent solution of dextrose (up to 100 cc) or smaller quantities of a 50 per cent solution.

Kulcke<sup>5</sup> reported a case of chronic pneumothorax of three months' duration in a 9 year old child. A satisfactory result was obtained in six weeks after three injections of a 30 per cent solution of dextrose given ten days apart (20 cc, 35 cc and 50 cc, respectively). Fogelberg and Wallgren<sup>6</sup> reported 2 clinical cures with the use of a 30 per cent solution of dextrose.

Brunner,<sup>7</sup> Kenner,<sup>8</sup> Schott<sup>9</sup> and Morlock<sup>10</sup> had no success with a 30 per cent solution of dextrose. Schott<sup>11</sup> obtained 2 clinical cures by using a 50 per cent solution of dextrose supplemented by temporary underwater drainage of the pneumothorax. Kenner<sup>8</sup> succeeded with 20 cc of a 0.5 per cent solution of silver nitrate after failing with a 30 per cent solution of dextrose.

Single cases in which treatment was successful were reported by Morlock,<sup>10</sup> who used 5 cc of a 1 per cent solution of silver nitrate; by Schott,<sup>9</sup> who used 0.5 cc of oil of turpentine, by Watson and Rob-

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1 Spengler, L. *Ztschr f Tuberk* 2:27, 1901

2 Spengler, L. *Beitr z klin Chir* 49:80, 1906

3 Spengler, L., in Brauer, L., Schroder, G., and Blumenfeld, F. *Handbuch der Tuberkulose*, Leipzig, J. A. Barth, 1919, vol 3, p 232

4 Spengler, L. *Schweiz med Wchnschr* 4:310, 1923

5 Kulcke, E. *Munchen med Wchnschr* 67:1175, 1920

6 Fogelberg, H., and Wallgren, I. *Finska lak-sallsk handl* 66:38, 1924

7 Brunner. *Mitt a d Grenzgeb d Med u Chir* 33:124, 1924

8 Kenner, A. *Beitr z Klin d Tuberk* 80:169, 1932

9 Schott, E. *München med Wchnschr* 81:716, 1934

10 Morlock, H. V. *Proc Roy Soc Med* 26:525, 1933

11 Schott, E. *Munchen med Wchnschr* 82:1751, 1935



ertson,<sup>12</sup> who used venous blood, and by Apostolidés and Hadjissarantos,<sup>13</sup> who used guaracol and iodoform. The use of a solution of silver nitrate and of oil of turpentine was followed by violent pleural reactions but led to ultimate cure.

Our review of the world literature disclosed the reports of no more than 12 cases of spontaneous pneumothorax treated by the induction of chemical pleuritis. The largest single series, comprising 3 cases, was reported by Schott.<sup>14</sup>

In the following report we shall describe the methods employed and the results obtained for 5 of 6 patients treated by us. The sixth left the hospital against advice before the treatment could be carried to completion. We shall also discuss the problems in pulmonary mechanics presented by these patients, especially their bearing on treatment. Obviously this series is too small to justify sweeping conclusions. We are of the opinion, however, that the value of the method has been demonstrated by the satisfactory results obtained in the 5 cases, namely, healing of the fistula and reexpansion of the lung.

#### REPORT OF CASES

**CASE 1** (service of Dr. B. S. Oppenheimer) —J. F., a 46 year old Italian barber, entered the Mount Sinai Hospital on Aug. 13, 1934, complaining of severe shortness of breath of two and a half months' duration.

He was well until one year before admission to the hospital, when he experienced a sudden sharp pain in the right side of the chest. This was followed by weakness, which lasted for several hours. Ten weeks before admission he had a similar attack while lifting a heavy object. The pain was agonizing. It radiated from the right axilla to the epigastrium and lasted one hour. Although the patient felt extremely weak, he continued to be up and about for two days, until he was forced to bed by increasing shortness of breath. He remained bedridden until he was hospitalized. At no time did he complain of cough, expectoration or fever.

On physical examination, he appeared well nourished, dyspneic and somewhat cyanotic. The dyspnea became more marked at the least effort. The trachea deviated to the left. The right side of the chest was hyperresonant, breath sounds were diminished, and fremitus was absent over the right lung. The heart was displaced to the left, and the apex was felt in the midaxillary line.

Roentgen examination of the chest (fig. 1A) revealed pneumothorax on the right, with almost complete collapse of the lung. The heart and the mediastinal structures were displaced to the left. There was no evidence of parenchymal pulmonary disease.

**Management** —The clinical features of the case were those of tense pneumothorax, which had apparently existed for over ten weeks. Manometric readings

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12 Watson, E. E., and Robertson, C. Recurrent Spontaneous Pneumothorax. Report of Three Cases, *Arch. Surg.* **16**: 431 (Jan., pt. 2) 1928.

13 Apostolidés, C., and Hadjissarantos, D. *Paris méd.* **1**: 338, 1930.

14 Footnotes 9 and 11.

of the intrapleural pressure on the right were made two days after admission and were found to be  $+9$  and  $+12$  cm of water on quiet inspiration and expiration, respectively. In order that the patient might obtain relief from his acute dyspnea, 1,300 cc of air was aspirated. This reduced the intrapleural pressure to  $-5$  cm and  $-1$  cm of water on quiet respiration. The relief afforded the patient was prompt but short lived. When manometric readings were taken one day later, they were  $+9$  and  $+11$  cm of water on quiet inspiration and expiration, respectively. Obviously the tense pneumothorax had been promptly reestablished through the persisting valvelike defect in the lung and the visceral pleura.

We realized that spontaneous closure of the defect was not likely to occur, and we decided to attempt a cure by the induction of chemical pleuritis. We chose iodized poppyseed oil as the substance to be used for the following reasons: 1 We were familiar with its innocuousness for lung tissue from our bronchographic work. 2 We were anxious to demonstrate that the pleuropulmonary communication was truly a one-way valve, so that the iodized oil would not be able to leave the pleural cavity and would not enter the parenchyma of the lung.



Fig 1 (case 1) —*A*, roentgenogram showing a large pneumothorax on the right, with almost complete collapse of the lung. Note the marked displacement of the mediastinal structures to the left. *B*, roentgenogram showing complete reexpansion of the right lung. Note the circumscribed opaque patch representing the iodized oil on the pleural surface.

One week after the patient's admission 10 cc of warmed iodized oil was injected into the right pleural cavity through an 18 gage needle attached to a Luer syringe. The skin and the wall of the chest were anesthetized in the usual manner by a 1 per cent solution of procaine hydrochloride. The patient received  $\frac{1}{6}$  grain (0.01 Gm) of morphine sulfate subcutaneously about fifteen minutes before the procedure was started. In order that the iodized oil might spread over as much of the pleural surface as possible, the patient was instructed to change his position frequently during a short period following the injection of the oil. He experienced relatively little discomfort immediately after the injection. However, within about one hour he complained of a sense of tightness in the right side of the chest. Three hours later his temperature rose to  $102.2^{\circ}\text{F}$ , and there was considerable pain in the right side of the chest. A blood count made at this time showed 10,600 white cells per cubic millimeter. However, within a few hours the discomfort in the chest decreased, and the next day the temperature dropped to normal. The patient was kept comfortable with the aid of sedatives. He was

instructed to remain on his right side as continuously as possible and to refrain from coughing, from talking loudly and from other effort which might increase the respiratory excursion

The object of these precautions was to keep the pleuropulmonary communication closed as continuously as possible and thus allow the inflammatory reaction to seal it. With the patient lying on the affected side the intrapleural pressure was raised to higher levels because of the effect of gravity on the mediastinal structures and because of the mechanical disadvantage of the respiratory muscles of the affected hemithorax. This was verified by manometric determination of the intrapleural pressure with the patient in various positions of recumbency. The importance of avoiding sudden increase in the inspiratory effort will also be readily appreciated. In order to keep the valvelike communication continuously closed, the intrapleural pressure must remain above the atmospheric pressure during the inspiratory phase of respiration. This is not difficult to accomplish during quiet respiration. However, a strong inspiratory effort may transform moderately positive pressure during quiet inspiration into negative pressure of a considerable degree and may thus result in the reopening of the valvelike defect in the lung which was tending to be sealed over by the inflammatory pleural reaction.

On the day following the injection of the iodized oil, a succussion splash could be elicited, and roentgen examination showed a small effusion. During the ensuing week the dyspnea progressively decreased. On the eighth day after the induction of the chemical pleuritis the manometric readings of the intrapleural pressure were  $-6$  cm and  $+1$  cm of water on quiet respiration. This indicated the probable closure of the valvelike defect in the visceral pleura and the lung. In order that this probability might be confirmed, 950 cc of air was aspirated. As expected, the manometric readings became more definitely negative ( $-8$  and  $-2$  cm). This last maneuver proved to be ill advised. It resulted in the reopening of the recently sealed defect, as was shown the next day, when the manometric readings on quiet respiration were  $+3$  and  $+8$  cm.

We therefore introduced another 10 cc of iodized oil into the pleural cavity in a second attempt to produce active chemical pleuritis. It is of interest that the local and the constitutional response to this were identical with those detailed in the description of the first injection of iodized oil. Thirteen days later the manometric readings on quiet respiration were  $-4$  cm and 0 cm. Roentgen examination made at this time showed considerable reexpansion of the right lung.

In order that the danger of reestablishing the pleuropulmonary communication might be avoided the patient was kept at rest in bed, remaining as quiet as possible. One week later the right lung showed 50 per cent reexpansion. The patient was allowed to leave the hospital and to continue his convalescence at home.

From this time reexpansion of the lung progressed uneventfully. Five weeks after the patient's discharge from the hospital (two months after the successful induction of chemical pleuritis) there was only a small residual hydropneumothorax. One month later the lung was completely reexpanded, the fluid was entirely absorbed, and the iodized oil appeared as a circumscribed opaque patch on the pleural surface. The patient remained entirely well. When seen three and a half years later he was in good health. He has had no recurrence of spontaneous pneumothorax (fig 1B). It is probable that the pleuritis has caused sufficient agglutination of the pleural surfaces to prevent recurrence of the pneumothorax which is so common in cases of the idiopathic type.

CASE 2 (service of Dr R Colp).—P. D., a 5 year old boy, was first admitted to the Mount Sinai Hospital on Jan 5, 1935, with postpneumonic pyopneumothorax on the left and purulent pericarditis. He was treated first by a stab

thoracotomy and then by rib resection and pericardiotomy. His clinical course was stormy and included the development of an empyema on the right, which also had to be drained. After the acute inflammatory process had been controlled, two serious complications became evident: (1) cardiac failure, apparently resulting from the pericardial process, and (2) pyopneumothorax on the left with a persistent bronchopleural communication. The cardiac failure was controlled by mercurial diuretics and digitalis. The pyopneumothorax was treated by drainage through a "flapper" tube. This tube allowed the drainage of pus and air during expiration but prevented the entrance of air during inspiration. After four months of hospitalization cardiac compensation was restored, drainage was discontinued, and the wound in the chest was allowed to heal. The child's condition improved sufficiently to permit his discharge from the hospital. However, in spite of the healing of the wound, the pneumothorax failed to absorb.

Two and a half months later the child was readmitted because of the persistence of the pneumothorax. After the healing of the wound in the chest the pneumothorax developed the characteristics of the tense form, with marked displacement of mediastinal structures toward the uninvolved side.

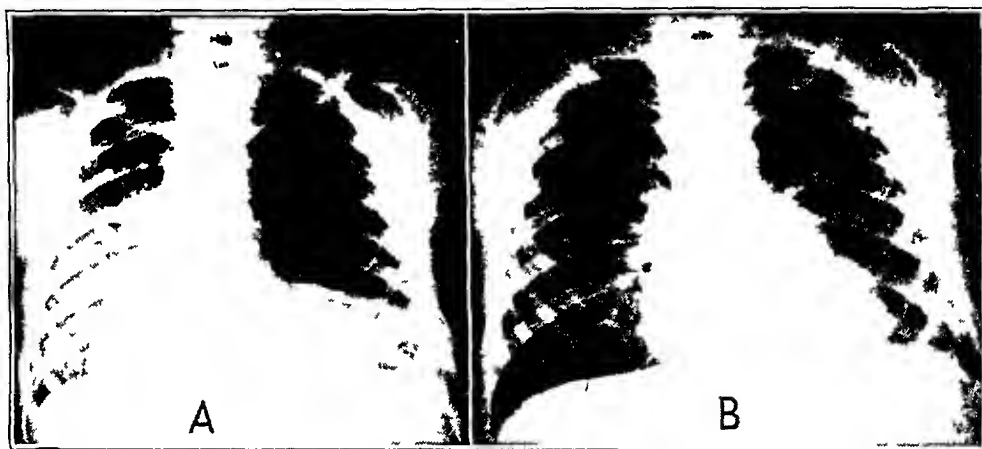


Fig 2 (case 2)—*A*, roentgenogram showing a large pneumothorax on the left. Note the marked herniation of the mediastinal structures into the right hemithorax. *B*, roentgenogram showing the complete reexpansion of the left lung. Note the small patches of iodized oil scattered over the pleural surface.

Physical examination at this time showed bulging of the left hemithorax, with greatly diminished respiratory excursions. There was tympany over the anterior aspect of the left side of the chest. The maximum cardiac impulse was felt and heard in the fourth intercostal space to the right of the sternum. Roentgen examination (fig 2 *A*) disclosed marked herniation of the mediastinal structures into the right hemithorax.

**Management**—It was obvious that chronic tense pneumothorax was present in this case. Measurement of the intrapleural pressure shortly after the child's admission showed manometric readings of  $+3$  and  $+12$  cm of water on quiet inspiration and expiration, respectively. These findings indicated the existence of a one way valve communicating between the pleural cavity and the lung. In order that this probability might be confirmed, 550 cc of air was aspirated from the left pleural cavity. A temporary reduction of the pleural pressure was obtained. However, after a few minutes of deep respiration the pleural pressure

was again  $+3$  and  $+8$  cm of water on quiet inspiration and expiration, respectively. This maneuver proved conclusively that a one way communication existed between the lung and the pleural cavity.

Because of the long duration of the process it was felt that spontaneous recovery was not likely to occur. It seemed doubtful whether the induction of chemical pleuritis would prove helpful in sealing over the valvelike defect in the lung and the visceral pleura. This pleura had been the seat of severe inflammatory reaction only a few months previously. It was therefore thought that it was not likely to respond to simple chemical irritation with inflammatory reaction sufficiently active to obliterate the chronic defect. However, since no other simple remedy was available, we decided to try this procedure. Accordingly, 10 cc of iodized oil was injected into the left pleural space with the technic previously described. The child did not complain of pain in the chest after this procedure. Twenty-four hours later the temperature rose from 99 to 100.4 F. Another rise, this time to 101 F, occurred six days later. On the sixteenth day the intrapleural pressure was 0 cm and  $+6$  cm of water on quiet inspiration and expiration, respectively. Roentgen examination two days later showed considerable absorption of the pneumothorax and partial return of the mediastinal structures to the central position. Subsequently absorption of the pneumothorax and reexpansion of the left lung continued without interruption. Seven weeks after the induction of the pleuritis, roentgen examination showed that the pneumothorax occupied about 33 per cent of the left pleural cavity and that the mediastinal structures had returned to the normal position. Within six months the lung had entirely reexpanded. Two and a half years later (the time of writing) the child was perfectly well, the left lung was fully reexpanded and showed no abnormality. The iodized oil could still be seen scattered in small patches over the pleura (fig 2B).

It is of interest that the iodized oil was able to produce a chemical pleuritis which effectively healed the chronic pleuropulmonary communication despite the fact that the pleura had previously been the seat of a severe inflammatory process. Apparently the initial acute pleuritis was not able to produce healing of the by-pass fistula which existed at the time, and the pleural inflammation had completely subsided before a check valve mechanism developed and the conditions became favorable for the permanent closure of the bronchial fistula. The acute inflammatory reaction evoked by the introduction of iodized oil into the pleural cavity produced freshening of the partially epithelized fistula and thus favored its healing after it had been kept closed for a while by the high intrapleural pressure which was present (as a result of the check valve mechanism which had developed in the meantime).

CASE 3 (service of Dr. B. S. Oppenheimer) —A S., a 15½ year old school girl, entered the Mount Sinai Hospital on Sept. 30, 1937, complaining of shortness of breath and of a nonproductive cough.

Two years before admission she began to have shortness of breath on little exertion. This was not progressive. She did not remember having experienced pain in the chest at any time. Six months before admission a nonproductive cough developed. At that time a school physician advised roentgen examination of the chest, but because of the mildness of the symptoms this advice was not

heeded During the past two months her cough had produced a small amount of whitish sputum There was also some loss of weight One week before the patient's admission roentgen examination of the chest was made and hospitalization was advised

Physical examination on admission revealed a well nourished young girl who was in no respiratory distress when at rest The right hemithorax moved little on respiration The trachea deviated slightly to the left The right side of the chest was hyperresonant The breath sounds over the right lung were diminished in intensity and had an amphonic quality The heart did not appear to be displaced

Roentgen examination (fig 3 *A*) revealed a large pneumothorax on the right with complete collapse of the lung The heart and the mediastinal structures were slightly displaced to the left

The sputum contained no tubercle bacilli The tuberculin reaction was negative

*Management*—This was obviously a case of chronic pneumothorax The probable duration of the condition could only be surmised It appeared certain



Fig 3 (case 3) —*A*, roentgenogram showing complete collapse of the right lung by a large pneumothorax The mediastinal structures are displaced slightly to the left *B*, roentgenogram showing almost complete absorption of the pneumothorax The lung has not as yet fully reexpanded The mediastinal structures are displaced considerably to the right, and the right leaf of the diaphragm is moderately elevated

that the pneumothorax was present six months before the girl's admission, at the time the school physician advised roentgen study of the chest Furthermore, it was most probable that the dyspnea, which was first noted two years before admission but was not progressive, was due to the pneumothorax present at that time

The chronicity of the process could be inferred from the history While the physical and roentgen findings did not suggest the existence of a tense pneumothorax, in view of the relatively insignificant displacement of the mediastinal structures, manometric readings showed the intrapleural pressure to be +2 and +3 cm of water on quiet inspiration and expiration, respectively The lack of displacement of the mediastinal structures indicated that they did not possess the normal degree of flexibility An antecedent inflammatory process involving the

mediastinal pleura was therefore suspected. Whether the process was related to underlying disease in the lung or was the result of the mechanical irritation of chronic pneumothorax could not be definitely determined.

*Management*—The finding of a positive intrapleural pressure on quiet respiration indicated that the pneumothorax was periodically renewed through a persistent one way bronchopleural communication. Because of the long duration of the pneumothorax a spontaneous cure was not likely to occur. We therefore decided to induce chemical pleuritis in an attempt to produce healing of the defect in the lung. Our experience in the first 2 cases, in which we had used iodized oil as the irritant, had been satisfactory enough to warrant repetition of this treatment. However, the iodized oil had shown one objectionable feature. It had failed to become absorbed. We therefore decided to use a 50 per cent aqueous solution of dextrose. Accordingly, 50 cc of such a solution was introduced into the space occupied by the pneumothorax. The patient experienced little discomfort either at the time of injection or at any time thereafter. There was no rise in temperature or change in the leukocytic picture. One week later the manometric readings were  $-5$  cm and 0 cm of water during quiet inspiration and expiration, respectively. At the same time roentgen examination showed the pneumothorax to be smaller and the right lung partially reexpanded. There was also a small pleural effusion. This was evidence that active pleuritis had been produced.

One month later it was noted that the lung, instead of reexpanding further, had again become completely collapsed. Apparently after the expansion of the lung had reached a certain point, the defect in the lung and the visceral pleura had reopened, with consequent recurrence of the original tense pneumothorax.

We therefore attempted to produce more acute pleuritis by injecting 60 cc of a 67 per cent solution of dextrose. This procedure was repeated two weeks later. The result was similar to that of the original injection. After temporary closure, the pleuropulmonary communication reopened when the reexpansion of the lung had reached a certain point.

We then decided to use iodized oil, in the hope that it would prove a more potent irritant. Twelve cubic centimeters of oil was injected into the right pleural cavity. The patient experienced considerable discomfort in the chest shortly after the injection. The next day her temperature rose to 101 F. The pain and fever subsided within forty-eight hours.

Two days later there was moderate pleural effusion, evidenced by a succussion splash. Manometric readings showed the intrapleural pressure to be  $-8$  cm and 0 cm on quiet inspiration and expiration, respectively. Roentgen examination at this time showed that the pneumothorax had decreased in size and that the right lung showed considerable reexpansion. Two months after the injection of the iodized oil there was marked decrease in the size of the pneumothorax, the lung reexpanded proportionately, and the manometric readings were  $-12$  and  $-4$  cm of water on quiet inspiration and expiration, respectively.

The regimen of sedatives and rest in bed with the patient lying on the involved side was continued throughout this period. Only after repeated observation had convinced us that the pleuropulmonary communication was safely closed was the patient allowed moderate activity. Roentgen examination six months after the injection of iodized oil (fig 3B) showed that the pneumothorax had almost completely disappeared, the lung had reexpanded in proportion and the effusion had been absorbed. However, it was noted that the mediastinal structures were considerably displaced to the right and that the right leaf of the diaphragm was elevated.

Apparently the visceral pleura had reacted to prolonged irritations with formation of so much fibrous tissue that complete reexpansion of the lung was prevented. Failure of the lung to reexpand completely had in turn caused the displacement of the mediastinum and of the right leaf of the diaphragm.

Although the lung had not returned to a state of full inflation, we feel that the therapeutic result achieved is most gratifying.

CASE 4 (service of Dr B S Oppenheimer) —H G, a 39 year old shoe salesman, entered the Mount Sinai Hospital on May 25, 1937, complaining of shortness of breath which had lasted nine months. Arterial hypertension had been discovered eight years previously, but it had caused relatively little disability. Nine months before admission to the hospital, while taking a shower bath, the man suddenly felt a severe stabbing pain in the right side of the chest. A physician who examined him by fluoroscope told him that he had pneumothorax on the right. The patient continued his usual activities, though he was disturbed by dyspnea on mild exertion. He was observed at regular intervals by his physician, and because of the persistence of the pneumothorax at the end of nine months he was hospitalized.

On admission the patient appeared well developed. He showed moderate dyspnea on little exertion. Physical and roentgen examination of the chest revealed a pneumothorax on the right with complete collapse of the lung. The heart was enlarged but was only slightly displaced to the left. The blood pressure was 260 mm of mercury systolic and 140 mm diastolic. There were no signs or symptoms of cardiac insufficiency.

*Management* —The diagnosis of chronic tense pneumothorax was made on the basis of the history and of the physical and the roentgen findings. This diagnosis was definitely established when the manometric readings of the intrapleural pressure were found to be  $+4$  and  $+10$  cm of water on quiet inspiration and expiration, respectively. The fact that the mediastinum was only slightly shifted to the left was due to the inflexibility of this structure, because of which the pneumothorax, although it was under considerable tension, produced little embarrassment to the patient. Although the tense pneumothorax appeared to cause little discomfort, it was felt that it would be a great gain if the function of the right lung could be restored.

We therefore decided to treat the patient by the induction of chemical pleuritis. Accordingly, 50 cc of a 50 per cent solution of dextrose was introduced into the right pleural cavity. As no evidence of pleuritis and no change in the size of the pneumothorax were noted after one week, 25 cc of a 67 per cent solution of dextrose was injected. There was no febrile reaction, but the patient complained of pain in the right side of the chest. Physical and roentgen examination gave evidence of moderate pleural effusion. Within one week the upper and the middle lobe of the right lung reexpanded to 40 per cent of their normal volume, and manometric readings showed  $-5$  and  $+4$  cm of water on quiet respiration, indicating closure of the pleuropulmonary communication. Several days later the right lung was found to have reexpanded 75 per cent. At this time the patient was allowed to be out of bed. This liberty was apparently premature. It resulted in the reopening of the pleuropulmonary communication, as shown by recurrence of the collapse of the lung and rise of the intrapleural pressure to  $+1$  cm and  $+6$  cm of water on quiet respiration. This experience emphasized that prolonged



rest in bed during the course of the active pleuritis is necessary to insure firm closure of the pleuropulmonary communication. The treatment was repeated, with 45 cc of a 67 per cent solution of dextrose. The patient was kept at strict rest in bed, which was supplemented by sedatives, for three weeks. During this period there was progressive reexpansion of the lung. Within one month it was almost completely reexpanded. The patient was then discharged from the hospital and allowed moderate activity. Six months later he was well, and roentgen examination of his chest showed no evidence of pneumothorax. The right lung showed no abnormality.

CASE 5 (service of Dr B S Oppenheimer) —M B, a 47 year old compositor and pressman, was admitted to the Mount Sinai Hospital on Jan 16, 1938, because of recurring attacks of severe dyspnea during the previous six months.

He had no previous history of significant pulmonary disease, and he had been in good health for many years prior to the onset of the present illness.

Early in July 1937 he experienced sudden severe pain in the left side of the chest after climbing a flight of stairs. The acute pain lasted only a few minutes, but it left him with considerable dyspnea on little exertion. A mild nonproductive cough developed. As these symptoms rapidly became worse, the patient consulted a physician. He was advised to rest in bed and was treated with digitalis. These measures afforded him no relief. Dyspnea and orthopnea became increasingly more distressing, and the patient had to be treated with inhalations of oxygen. At this time roentgen examination of the chest showed evidence of a large pneumothorax on the left and of bilateral tuberculosis of the upper lobes. The patient was therefore sent to an institution for the tuberculous.

At the time of his transfer to the sanatorium the patient's respiratory distress was so marked that oxygen therapy had to be administered during the journey of a hundred miles (160 kilometers). On arrival at the sanatorium aspirations of air were employed several times, at intervals twelve to thirty-six hours apart, to afford the patient relief from severe dyspnea.

The acute symptoms subsided after a few days' stay in the sanatorium. Because of a suspicion of active tuberculous disease it was decided to maintain the pneumothorax at low tension by small refills administered every three or four days. However, when after three months of observation the various studies failed to disclose evidence of active tuberculosis, the left lung was allowed to reexpand. The patient was permitted increasing amounts of activity during the succeeding two months and was discharged from the sanatorium apparently well at the end of a five months' stay.

Three weeks later he experienced a sudden recurrence of suffocative dyspnea and was admitted to the Mount Sinai Hospital with the diagnosis of recurrent pneumothorax on the left.

On admission the patient showed marked dyspnea and orthopnea, which were greatly increased on the least effort or excitement. The physical signs in the lungs were those of tense pneumothorax on the left with considerable displacement of the mediastinal structures to the right. The heart rate was 120 per minute, and there was definite evidence of cardiac embarrassment. The blood pressure was 150 mm of mercury systolic and 96 mm diastolic. The venous pressure was 105 cm, rising to 115 cm on pressure on the right upper quadrant. The saccharin circulation time was eighteen seconds.

Roentgen examination (fig 4A) showed a large pneumothorax on the left which collapsed the left lung and displaced the mediastinum considerably to the

right The upper lobe of the right lung was shrunk as a result of a fibrotic tuberculous process, and the lower lobes showed fibrotic strands, marked emphysema and emphysematous blebs

*Management*—The diagnosis of recurrent tense pneumothorax was obvious The manometric readings in the left pleural cavity during quiet respiration were + 6 and + 20 cm of water on inspiration and expiration, respectively The patient appeared nervous on admission and was much alarmed by his symptoms Having obtained relief from aspiration of air on previous occasions, he was pleading for this treatment The futility of the procedure was explained to him He was advised to remain as quiet as possible and to refrain from exaggerated respiratory effort in order to avoid the marked rise in intrapleural pressure which was responsible for his distress However, it was not possible to keep him sufficiently quiet the first few days, and aspiration of about 300 cc of air had to be performed several times to give him relief from the recurring acute symptoms

Since the patient had spontaneously recovered from pneumothorax five months previously, spontaneous cure might have been anticipated on this occasion as well



Fig 4 (case 5)—*A*, roentgenogram showing a large pneumothorax on the left, with collapse of the left lung and considerable displacement of the mediastinum to the right Note the fibroid tuberculous lesion in the upper lobe of the right lung and the emphysematous blebs in the lower lobes *B*, roentgenogram showing the left lung completely reexpanded Note the extensive emphysematous changes with formation of blebs in the reexpanded left lung

However, we decided to treat him by the induction of chemical pleuritis for the following reasons 1 Spontaneous cure might not take place again 2 Closure of the pleuropulmonary communication might be achieved more quickly by induced pleuritis 3 The induced pleuritis might result in agglutination of the pleural surfaces and thus prevent recurrence of tense pneumothorax, which had been so distressing

The technic employed in the preceding cases was used First 50 cc of a 50 per cent solution of dextrose was used, but without success However, effective pleuritis was induced by injection of 65 cc of a 67 per cent solution of dextrose into the cavity of the pneumothorax Nine days later the pleural pressure fell to -3 and +7 cm of water on quiet respiration, and fluoroscopic study showed considerable resorption of the pneumothorax After four weeks the left lung was almost completely reexpanded From that time the patient's progress continued without interruption, and he was soon able to resume normal activity

When last seen, in June 1938, he was well. The left lung had remained fully reexpanded. Roentgen examination showed the left lung, as well as the right, to be the seat of a fibrotic tuberculous process in the upper lobe and of extensive emphysematous changes with formation of blebs in the lower lobe (fig 4 B).

It is probable that the rupture of one of these emphysematous blebs was responsible for the recurrent valvular pneumothorax in the past, and it is hoped that the induced pleuritis may prevent such recurrences in the future.

#### COMMENT

The cure of tense pneumothorax will take place as soon as the pleuropulmonary communication has permanently healed. Healing will depend on two factors: (1) the maintenance of a positive intrapleural pressure to keep the opening closed during both phases of respiration and (2) the production of a pleural reaction sufficient to seal the opening permanently. These are the objectives in the management of chronic tense pneumothorax. The 5 cases show how these objectives have been obtained under varying conditions. They also demonstrate how much the treatment depends on correct understanding of the underlying mechanism. These aspects of the subject merit some general comment.

*Mechanism*—The existence of chronic pneumothorax presupposes the presence of a persistent pleuropulmonary communication. This communication may be either a two way or a one way valve. With a pleuropulmonary communication of the two way type, air can enter the pleural cavity during inspiration and leave it during expiration. This will occur if the defect in the lung is relatively large and stiff walled. Under such circumstances the pleural pressure is a few centimeters of water below 0 during inspiration and an equal number of centimeters above 0 during expiration. Whether the mediastinum is displaced under these conditions depends on its relative flexibility. With a flexible mediastinum marked displacement may occur even with low pleural pressure, and the condition may simulate true tense pneumothorax in every detail. Whether our present method of treatment will prove adequate for a condition of this type is problematic and can be determined by trial only; a patient with such an involvement has recently come under our care, and the result of treatment will be reported at a later date.

When the pleuropulmonary communication is of the one way, or check valve, type, air can enter the pleural cavity during inspiration if the intrapleural pressure created is below the atmospheric pressure, but cannot leave it during expiration when the pleural pressure is above the atmospheric pressure. The size and tension which the pneumothorax can attain under such circumstances will depend primarily on the forcefulness of the inspiratory effort and only to a lesser extent on the flexibility of the mediastinum. The opening and closing of the one way valve is automatically determined by conditions of pressure in the pneu-

mothorax cavity When the pressure is high enough, the valve remains closed during both phases of respiration The pneumothorax cavity is then closed, and air is absorbed from it according to the principles governing absorption of air in such a case As air is absorbed and the pressure in the pleural cavity falls progressively, a point is soon reached where it becomes lower than the atmospheric pressure during the inspiratory phase of respiration More air can enter the pleural cavity, thus renewing and perpetuating the tense pneumothorax Coughing, laughing and excitement, with attendant forceful inspiratory effort, are important factors in the recreation and maintenance of the tense pneumothorax It is because of these considerations that one of the objectives in the management of this condition is to maintain a positive intrapleural pressure to keep the opening closed during both phases of respiration This will be discussed later, when accessory measures are considered

The severity of the symptoms produced by a tense pneumothorax is determined in addition by the integrity of the functioning lung, the flexibility of the mediastinum and the condition of the heart This was well illustrated in the fourth and the fifth case In case 5 there was a marked degree of respiratory and cardiac embarrassment In case 4 these symptoms were mild, despite the facts that the size and tension of the pneumothorax were greater in this case and that there was, in addition, associated marked arterial hypertension This apparent discrepancy may be explained by the following circumstances In case 5 the function of the sound lung was greatly reduced by the disseminated fibrosis and emphysema as well as by the encroachment of the flexible mediastinum In addition, there was in this case latent myocardial insufficiency (as a result of chronic pulmonary disease and of independent disease of the coronary arteries) By contrast, in case 4 the functioning lung was in a healthy state, the mediastinum was relatively inflexible, and the heart was apparently in good condition

*Management*—In describing the management of these cases we emphasized the importance of the accessory measures which we employed in addition to the induction of chemical pleuritis These included rest in bed with the patient lying on the affected side, judicious use of sedatives and avoidance of undue inspiratory effort The object of the accessory procedures was to keep the pleuropulmonary communication closed during both phases of respiration The rationale was discussed in detail in connection with case 1

The question of aspiration of air also received due consideration The futility and harmfulness of this procedure have been repeatedly demonstrated in connection with the management of the pneumothorax in 4 of the 5 cases There should be no occasion to aspirate even small amounts of air for the relief of acute symptoms if the correct general regimen is followed

In general, it must be stressed that scrupulous attention to the details of the described regimen is essential if one is to secure the desired results, namely, the permanent closure of the fistula and the reexpansion of the lung.

As to the choice of the agent for inducing chemical pleuritis, we are inclined to limit ourselves for the present to a 67 per cent aqueous solution of dextrose in amounts varying from 50 to 60 cc and to iodized oil in amounts of 10 to 12 cc. While a 50 per cent aqueous solution of dextrose may be inadequate, a 67 per cent solution (saturated) is more likely to produce effective pleuritis, and it is just as safe as the less concentrated solution. It appears to us that the amount of solution used is less important than its concentration. We have used as little as 25 cc and as much as 60 cc with equally satisfactory results. The size of the pneumothorax cavity has been a rough guide to the amount of dextrose solution required, and 50 cc was the average quantity used.

When a saturated solution of dextrose failed to produce a cure in 1 of our cases, the use of iodized oil proved effective. The latter substance produced a much more acute reaction, as shown by thoracic discomfort, by a greater amount of effusion (which also appeared more promptly) and by constitutional symptoms.

It must be borne in mind that it was frequently necessary to repeat the injection if one attempt had failed, this was true of both a solution of dextrose and iodized oil. In the sixth case, which we did not report, both a solution of dextrose and iodized oil failed to produce a cure. However, had this patient not left the hospital against advice, further attempts would have been made to induce effective pleuritis, either by using iodized oil again or by employing a still more active irritant.

Whether we could have ultimately succeeded in that case cannot be stated with any degree of assurance. That our method will not succeed in all cases of chronic tense pneumothorax cannot be doubted. We are of the opinion, however, that the satisfactory results obtained in 5 of our 6 cases definitely established the value of the method.

#### SUMMARY

Tense pneumothorax results when a pleuropulmonary communication acts as a one way valve, allowing air to enter the pleural cavity during inspiration and preventing its escape during expiration.

Anything that will increase the inspiratory effort of the patient (dyspnea, cough, etc.) will allow more air to enter the pleural cavity, increasing the size and tension of the pneumothorax and thus aggravating the symptoms.

In most instances tense pneumothorax cures itself. When sufficient air enters the pleural cavity, the lung collapses, and the valvelike defect is closed. Healing of this defect will result if the collapse of the lung can be maintained by a moderately positive intrapleural pressure during inspiration as well as during expiration. Air in the pleural cavity acts as an irritant and usually produces sufficient inflammatory reaction to seal the defect. Once the pleuropulmonary communication is permanently closed, the pneumothorax will be absorbed, and the lung will reexpand.

Occasionally the tense pneumothorax persists in a chronic form for months or years, and the victim remains a chronic invalid because of the respiratory and cardiac embarrassment which he may suffer on little exertion.

By the induction of chemical pleuritis of greater or lesser severity it has been possible to produce healing of the chronic pleuropulmonary communication. A clinical cure occurred in 5 of 6 cases in which this method was tried. In the sixth case the patient left the hospital before the treatment could be completed.

Iodized oil and a concentrated solution of dextrose were used as the chemical irritants. The technic employed is described in detail in the case reports.

The following accessory measures are essential to keep the pleuropulmonary communication closed so that it may be permanently sealed by the induced chemical pleuritis: prolonged rest in bed, with the patient lying on the affected side; the judicious use of sedatives; the suppression of all acts attended by increased respiratory effort, and the avoidance of aspiration of air.

The mechanism underlying tense pneumothorax and its cure has been discussed in detail because of the important bearing it has on treatment.

# SEDIMENTATION RATE AND NONFILAMENT-FILAMENT RATIO IN LOW GRADE CHRONIC ILLNESS

A STATISTICAL ANALYSIS OF 292 CASES

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Although many articles have appeared on the variations in the sedimentation rate and nuclear count, little has been written on these subjects in relation to low grade chronic diseases, except tuberculosis and chronic arthritis, which have been studied extensively, and ulcerative colitis, concerning which an article has recently been published <sup>1</sup>

The sedimentation rate has been reported as normal in focal infections,<sup>2</sup> muscular rheumatism<sup>3</sup> and peptic ulcer without complications<sup>4</sup> Sjogren<sup>5</sup> reported that its determination was "useful in latent infections of the eye"

In regard to nuclear counts, it has been stated that in "all important focal infections"<sup>6</sup> and "long-continued or low-grade infection"<sup>7</sup> there is a rise in the Schilling index and that there is "in chronic conditions a persistent high shift,"<sup>8</sup> and there have been such conflicting statements

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1 Garvin, R O, and Bargen, J A The Hematologic Picture of Chronic Ulcerative Colitis, *Am J M Sc* **193** 744 (June) 1937

2 Merritt, W A The Sedimentation Rate in General Practice, *Minnesota Med* **20** 99 (Feb) 1937 Biern, O B Value of the Sedimentation Rate in Medicine, *West Virginia M J* **33** 289 (July) 1937

3 Schulten, H The Determination of the Sedimentation Rate of the Red Blood Corpuscles and Its Importance in Internal Medicine, *Med Klin* **27** 125 (Jan 23) 1931

4 Schindler, J A, and Gnagi, W B, Jr The Sedimentation Rate in General Practice, *Wisconsin M J* **34** 531 (Aug) 1935

5 Sjogren, H Blood Picture and Sedimentation Reaction in Inflammatory Diseases of Eye, *Hygiea* **97** 262 (April 15) 1935

6 Griffith, W H The Schilling Hemogram in Acute Infections, *Journal-Lancet* **57** 239 (June) 1937

7 Crocker, W J, and Valentine, E H Hemography in Diagnosis, Prognosis, and Treatment Based on Six Thousand Schilling Hemograms, *J Lab & Clin Med* **20** 172 (Nov) 1934

8 Gradwohl, R B H The Schilling Blood Methods, *South Med & Surg* **94** 53 (Feb) 1932

as that of Rosenfeld,<sup>9</sup> that in chronic appendicitis the blood picture is normal, and that of Crocker and Valentine,<sup>10</sup> that in chronic fibrous appendicitis the total number of shift cells ranges from 10 to 35, with a Schilling index of  $\frac{1}{4}$  to 1<sup>10</sup>

The present study was undertaken to determine the extent of variation in sedimentation rate and nuclear count in patients with chronic low grade diseases

#### CLINICAL DATA

Studies of the blood were made on 292 patients with chronic or frequently recurring symptoms, many of which were possibly secondary to low grade chronic infections. The patients studied, with few exceptions, were ambulant. While all age groups were included, the youngest patient studied being 2 years old and the oldest over 80, the majority of patients were young adults.

Of the 292 patients, most of whom had more than one disease, there were 146 with classic evidence of chronic sinusitis. Among the remainder, careful questioning and examination revealed the presence in 131 of such abnormalities as nasal congestion, postnasal discharge and inflammation of the nasopharynx, which Burbank<sup>11</sup> called evidence of chronic nasopharyngitis. If the criteria of such writers as Chase<sup>12</sup> are accepted, the latter group would also be classified as having chronic sinusitis. Of the total number of patients, 131 complained of frequent "colds."

Thirteen patients had chronic infections of the ear or mastoid, and 52 had chronic bronchitis, but only 10 showed evidence of chronic tonsillitis, and only 15, evidence of other oral infection. The low incidence of oral infection was probably due to the fact that the tonsils had previously been removed and the teeth had had excellent care in most cases.

There were 41 cases of colitis, 37 of other chronic or recurrent gastrointestinal conditions and 75 in which symptoms were referable to the biliary tract. Infections of the urinary tract occurred in 36 cases and prostatitis in 9. There were 14 cases of rheumatoid arthritis, 26 of other forms of arthritis, 7 of bursitis and 36 of "rheumatism," the

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9 Rosenfeld, E. B. The Clinical Significance of Schilling's Hemogram, *Vrach gaz* **31** 175, 1927

10 Crocker, W. J., and Valentine, E. H. Hemography in the Diagnosis of Appendicitis Based on Five Hundred Cases, *J. Lab. & Clin. Med.* **21** 883 (June) 1936

11 Burbank, R. Chronic Arthritis, *J. A. M. A.* **99** 1489 (Oct. 29) 1932

12 Chase, W. D. Etiology and Diagnosis of Sinusitis, *Pennsylvania M. J.* **39** 389 (March) 1936



patients having fleeting pains in the joints, muscular pain, stiffness and similar symptoms, which have been called "prodromes to arthritis"<sup>13</sup>

Of the aforementioned conditions, in which infection is rather generally considered to play a part, at least one was present in each patient. In addition 4 patients had nephritis, 14 migraine, 18 duodenal ulcer, 3 urticaria, 16 asthma, 16 hay fever, 3 eczema, 2 vasomotor rhinitis, 4 diabetes, 1 Ménière's disease and 3 thyrotoxicosis.

Patients were grouped according to severity of illness as having mild or recurrent, moderately severe or severe symptoms. An additional group included patients the severity of whose symptoms was more or less acutely increased above the customary level. In assigning patients to a group opinions were based on the severity of the disease process, rather than on subjective symptoms, psychogenic factors being discounted as far as possible.

#### METHODS

Routine blood counts and determinations of sedimentation rate were made on all patients. Variations in the sedimentation rate and in the nuclear count were the most frequent changes noted and are reported here. Since most of the nuclear counts showed not only an increase in the percentage of nonfilamented cells but a decrease in the percentage of filamented cells, it was thought that the ratio between nonfilamented and filamented neutrophils gave a better representation of the neutrophilic change than the percentage of nonfilamented cells alone.

In making differential blood counts neutrophilic leukocytes were divided into nonfilamented and filamented types according to the criterion of Haden,<sup>14</sup> i. e., "neutrophils in which two or more lobes are united only by a filament of chromatin material are recorded as filamented cells, all others are classified as nonfilamented." The ratio of nonfilamented to filamented neutrophils (referred to as the "nonfilament-filament ratio") was expressed in percentages,  $(\frac{\text{nonfilamented cells} \times 100}{\text{filamented cells}})$

The sedimentation rate was determined by the method of Westergren. About 2 cc of venous blood was introduced into a small vial containing a pinch of lithium oxalate. After gentle agitation the blood was drawn up to the 200 mm mark on a Westergren tube. At the end of one hour the height of the column of clear fluid was recorded in millimeters. Dry lithium oxalate was considered a satisfactory anticoagulant since in a control series of tests with dry potassium oxalate, which was not considered to increase the sedimentation rate above that obtained with heparin,<sup>15</sup> the results were parallel except that in the higher ranges, above 30 mm, the readings with lithium oxalate averaged 5 to 10 mm lower than those

13 Hench, P. S., Bauer, W., Fletcher, A. A., Ghrist, D., Hall, F., and White, P. The Present Status of the Problem of "Rheumatism," *Ann Int Med* 8 1517 (May) 1935.

14 Haden, R. L. Qualitative Changes in Neutrophilic Leukocytes, *Am J Clin Path* 5 354 (Sept) 1935.

15 (a) Bannick, E. G., Gregg, R. O., and Guernsey, C. M. The Erythrocyte Sedimentation Rate, *J A M A* 109 1257 (Oct 16) 1937. (b) Wintrobe, M. M., and Landsberg, J. W. Standardized Technic for Sedimentation Test, *Am J M Sc* 189 102 (Jan) 1935. (c) Greisheimer, E. M., Hodapp, A., and Goldsworthy, E. Effect of Anticoagulants on Sedimentation Rate, *ibid* 190 775 (Dec) 1935.

with potassium oxalate. In agreement with Bannick, Gregg and Guernsey<sup>15a</sup> and with Cutler, Park and Herr,<sup>16</sup> it was believed that correction for anemia was unnecessary. No cases of marked anemia were included in the study.

In all but a few cases two or more observations of the sedimentation rate and of the nonfilament-filament ratio were made, and the average was calculated. This tended to minimize any increase in the sedimentation rate due to apprehension or excitement at the time of the initial examination.<sup>17</sup> If the initial readings had

*Statistical Analysis of Nonfilament-Filament Ratios and Sedimentation Rates Distributed According to Sex, Age, Disease and Severity of Symptoms \**

Group	Nonfilament Filament Ratio, %					Sedimentation Rate, Mm				
	No	Median	Mean	S D	S E	No	Median	Mean	S D	S E
All patients	270	22.50	25.20	10.79	0.657	262	12.10	15.90	13.85	0.857
Sex										
Female	173	22.36	25.74	11.42	0.906	163	14.73	17.52	13.38	1.014
Male	97	21.89	24.60	10.32	1.081	93	7.56	13.24	14.51	1.501
Age										
1-10	17	25.50	26.53	12.10	2.94	10	15.50	15.50	10.08	3.19
11-20	23	26.05	23.09	15.77	3.29	15	10.50	16.00	14.69	3.79
21-30	45	21.57	22.56	8.48	1.26	41	5.50	9.10	8.92	1.39
31-40	52	21.33	25.21	11.33	1.57	54	12.44	16.52	14.80	2.03
41-50	72	21.97	23.42	8.60	1.13	68	12.25	14.47	11.41	1.38
51-60	37	21.50	23.68	13.00	2.14	35	14.66	19.71	17.31	2.90
61+	23	25.50	26.48	13.14	2.74	24	20.14	25.62	16.20	3.31
Severity of symptoms										
Mild	116	18.19	18.56	4.82	0.448	119	6.09	7.20	4.72	0.433
Moderate	98	23.45	24.22	6.47	0.654	88	20.59	19.99	9.36	0.99
Severe	36	38.71	40.10	10.94	1.82	34	35.22	39.91	15.69	2.78
Acutely exacerbated	20	42.58	44.00	10.46	2.34	20	8.42	9.50	6.92	1.55
Disease										
Sinusitis	135	22.61	25.43	11.33	0.972	131	10.90	14.83	12.47	1.09
Nasopharyngitis	122	21.80	24.39	10.02	0.906	120	14.17	17.37	14.62	1.34
Recurrent colds	119	23.09	26.18	11.47	1.027	111	10.40	14.81	12.87	1.25
Tonsillitis	19	24.50	29.05	12.96	2.96	19	18.00	21.16	17.53	4.02
Oral infections	15	19.07	19.33	4.66	1.20	16	16.00	14.25	10.79	2.70
Bronchitis	49	24.67	25.86	8.57	1.22	40	16.00	17.12	14.87	2.35
Gastrointestinal symp- toms	37	23.50	24.86	10.78	1.79	30	9.11	13.84	13.97	2.56
Colitis	37	29.50	31.38	13.12	2.16	28	10.22	17.11	16.45	3.12
Biliary	71	22.00	22.79	8.83	1.036	71	9.71	13.35	11.82	1.40
Urinary infection	31	25.50	27.84	12.32	2.22	34	19.67	19.47	13.03	2.24
Rheumatoid arthritis	14	36.75	36.93	16.33	4.37	15	33.00	37.33	18.34	4.74
Other arthritis	24	21.75	24.67	11.97	2.45	25	16.50	16.40	9.67	1.93
Rheumatism	36	21.33	24.38	10.94	1.82	32	10.25	15.97	13.98	2.47
Duodenal ulcer	18	19.68	22.16	7.50	1.77	17	7.17	8.89	7.33	1.78
Asthma	16	24.87	25.50	9.51	2.38	15	10.50	14.33	10.08	2.60

\* No indicates number of cases, S D, standard deviation, S E, standard error, biliary, symptoms referable to the biliary tract.

been used, the means and the ranges would have been considerably higher. A similar condition was found in regard to the nonfilament-filament ratio, although it has been said that the nuclear count is not affected by excitement.<sup>18</sup>

16 Cutler, J. W., Park, F. R., and Herr, B. S. The Influence of Anemia on Blood Sedimentation, *Am J M Sc* **195** 734 (June) 1938.

17 van Antwerp, L. D. Repeated Sedimentation Tests, *Am J Dis Child* **48** 814 (Oct) 1934. Cutler, J. W., and Cohen, L. The Blood Sedimentation Test as a Routine Procedure in the Tuberculosis Dispensary, *Am Rev Tuberc* **21** 347 (March) 1930.

18 Katz, H. L., and Nice, L. B. The Relation of the Nonfilament and Filament Counts During Excitement, *J Lab & Clin Med* **21** 1145 (Aug) 1936.

## RESULTS

The frequency distributions of the sedimentation rates and non-filament-filament ratios for all cases are shown in chart 1. Nonfilament-filament ratios ranged from 8 to 70, with a mean of 25.2. Sedimentation rates ranged from 2 to 80 mm, with a mean of 15.9 mm. Median

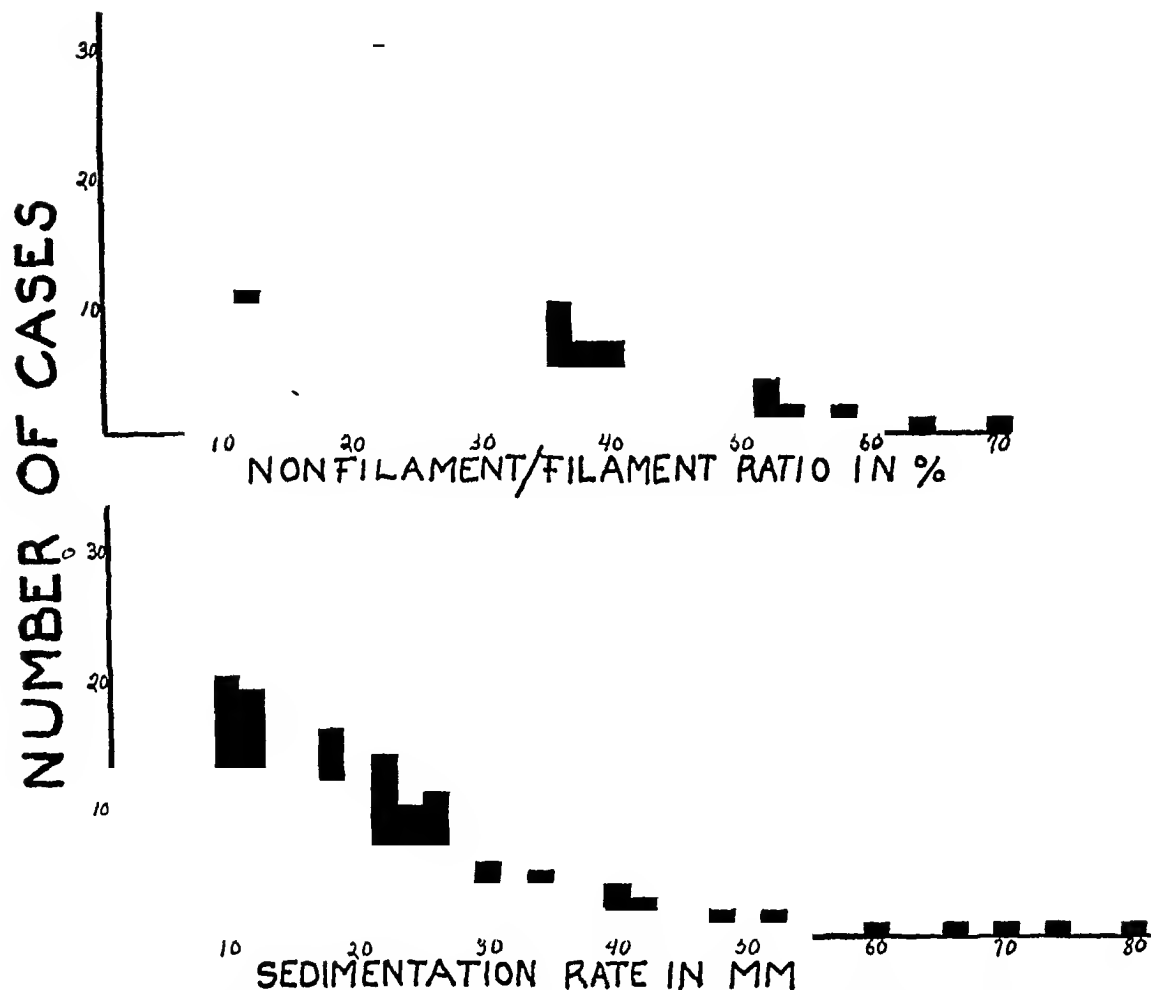


Chart 1—Frequency distribution of nonfilament-filament ratios and sedimentation rates for all cases

and mean values, with standard deviations and standard errors, are recorded in the table

When the observations were distributed according to sex (chart 2), the mean sedimentation rate for females was 17.52 mm, as compared with 13.24 mm for males, the difference being 2.68 times its standard error. There was no significant difference in the nonfilament-filament ratios.

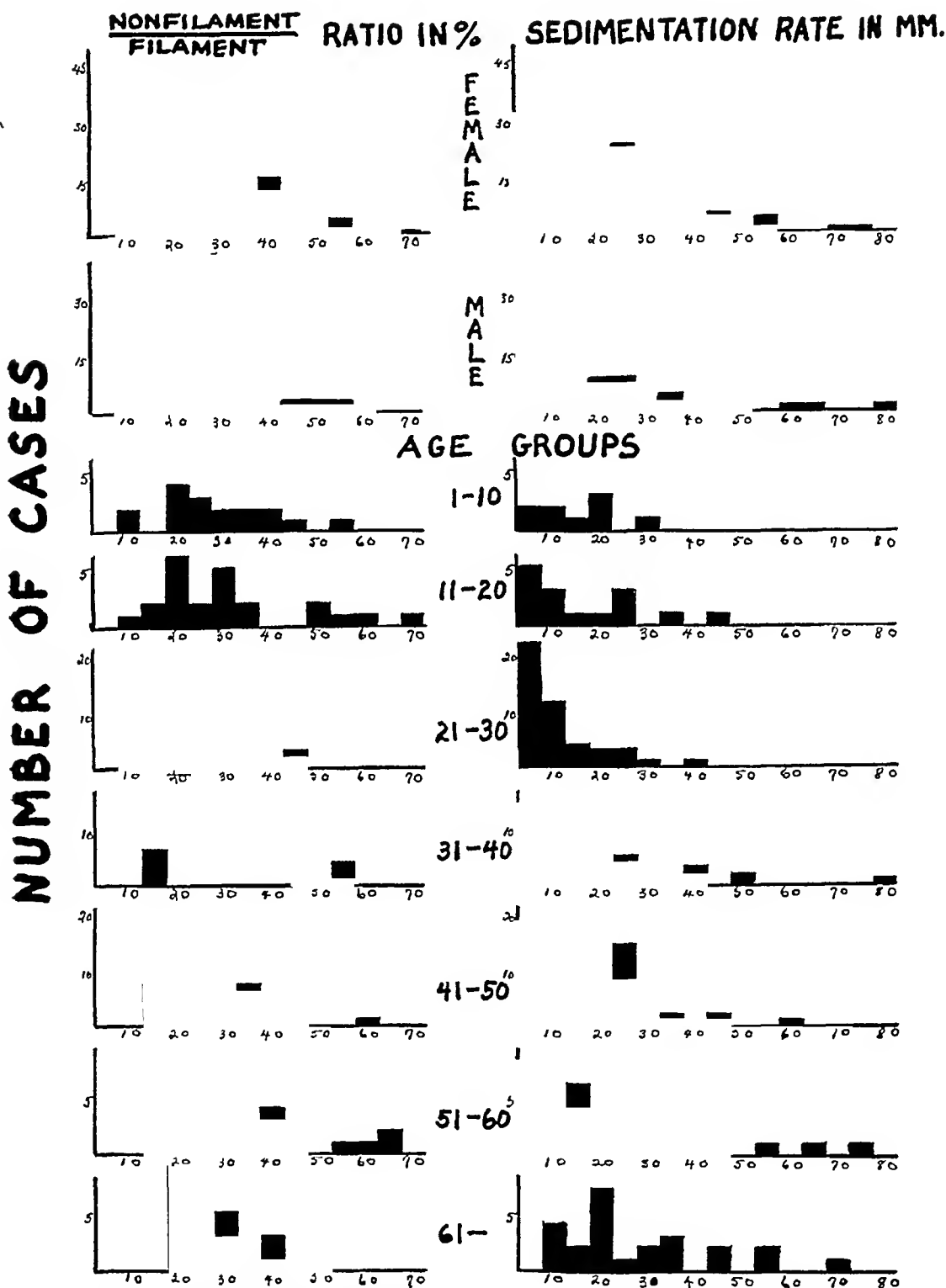


Chart 2—Nonfilament ratios and sedimentation rates distributed according to sex and age

When distributed according to age (chart 2), the mean nonfilament-filament ratios showed some variation, but in no case did the mean for any group differ from the mean for all cases by as much as 2.5 times the standard error of the difference. Sedimentation rates showed a somewhat greater variation. The mean for the group aged 21 to 30

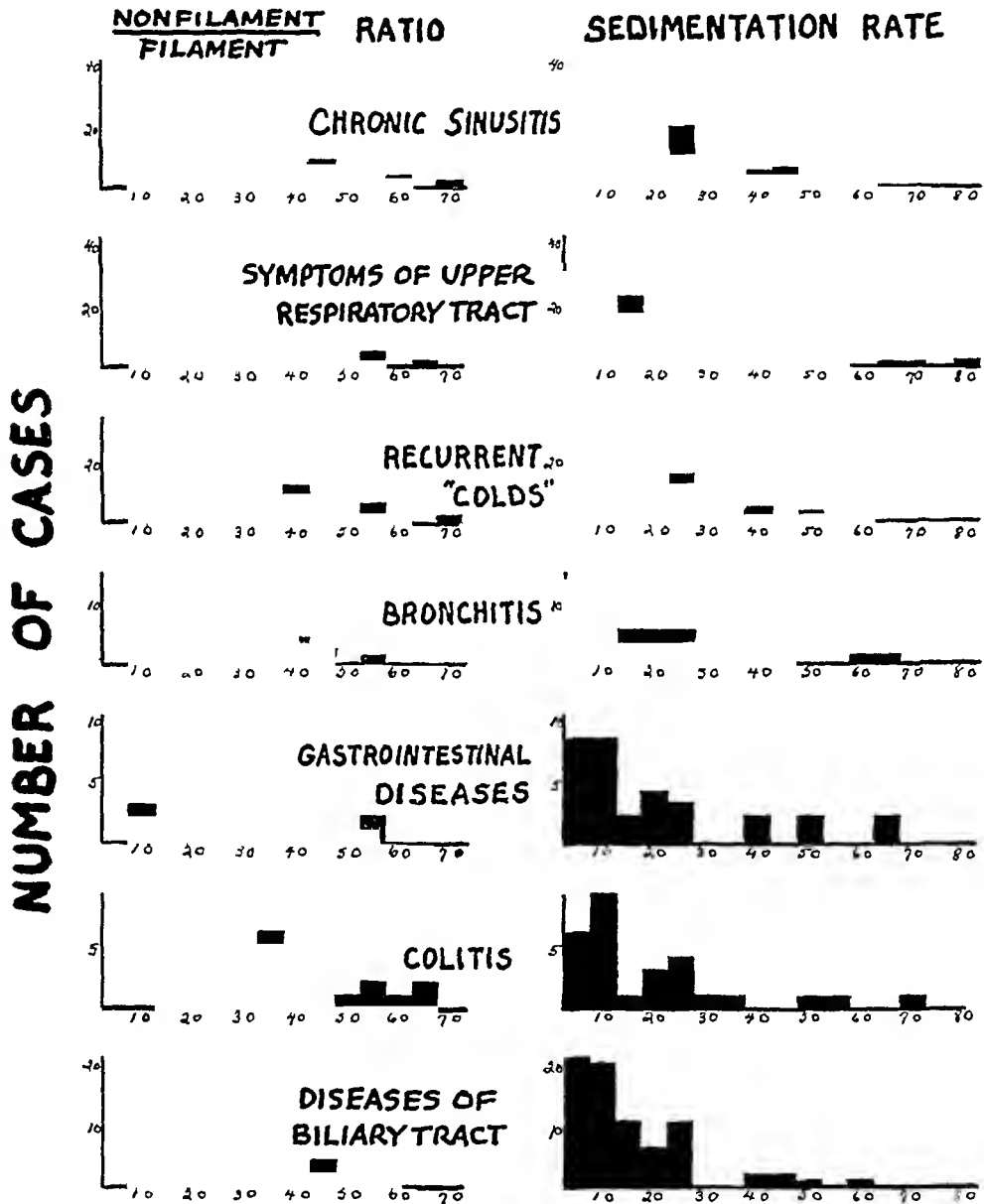


Chart 3—Nonfilament-filament ratios and sedimentation rates in cases of sinusitis, nasopharyngitis (symptoms of the upper respiratory tract), recurrent colds, bronchitis, colitis, other gastrointestinal diseases and diseases of the biliary tract

years was 9.1 mm (table), the difference from the mean for all cases being 4.53 times its standard error. The mean for the group over 60

was 25.9 mm, the difference from the mean of the entire series being five times its standard error. These differences were probably due less to age than to other factors which will be discussed later.

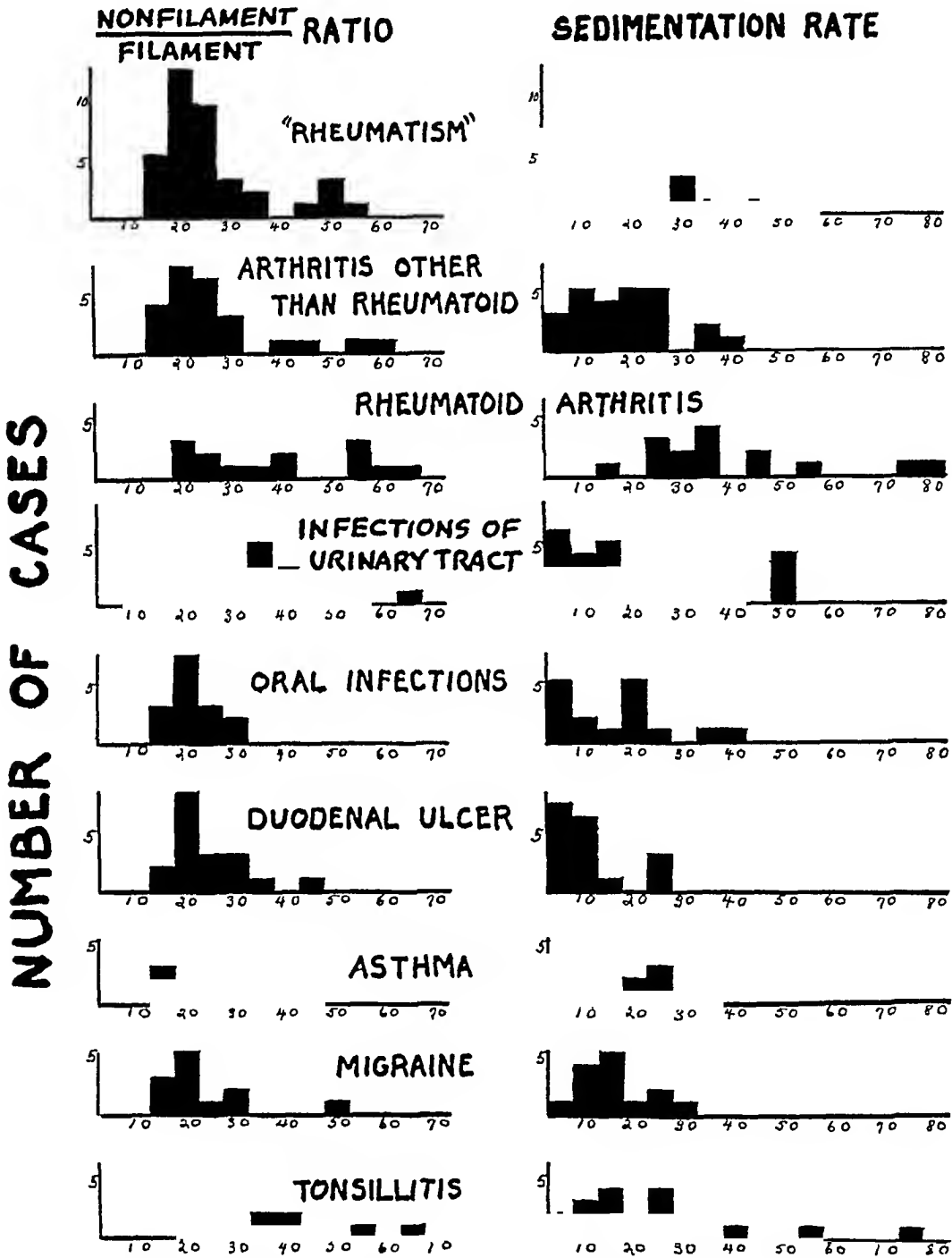


Chart 4—Nonfilament-filament ratios and sedimentation rates in cases of "rheumatism," rheumatoid arthritis, other forms of arthritis, infections of the urinary tract, oral infections, duodenal ulcer, asthma, migraine and tonsillitis

When the findings were distributed according to disease (charts 3 and 4), in cases of sinusitis, nasopharyngitis, recurrent colds, bronchitis, gastrointestinal conditions other than colitis, symptoms referable to the

biliary tract, infections of the urinary tract, prostatitis, rheumatism, arthritis other than the rheumatoid form and asthma, there were no significant differences from the general averages. In cases of tonsillitis, infection of the ear and mastoid and migraine there were minor devia-

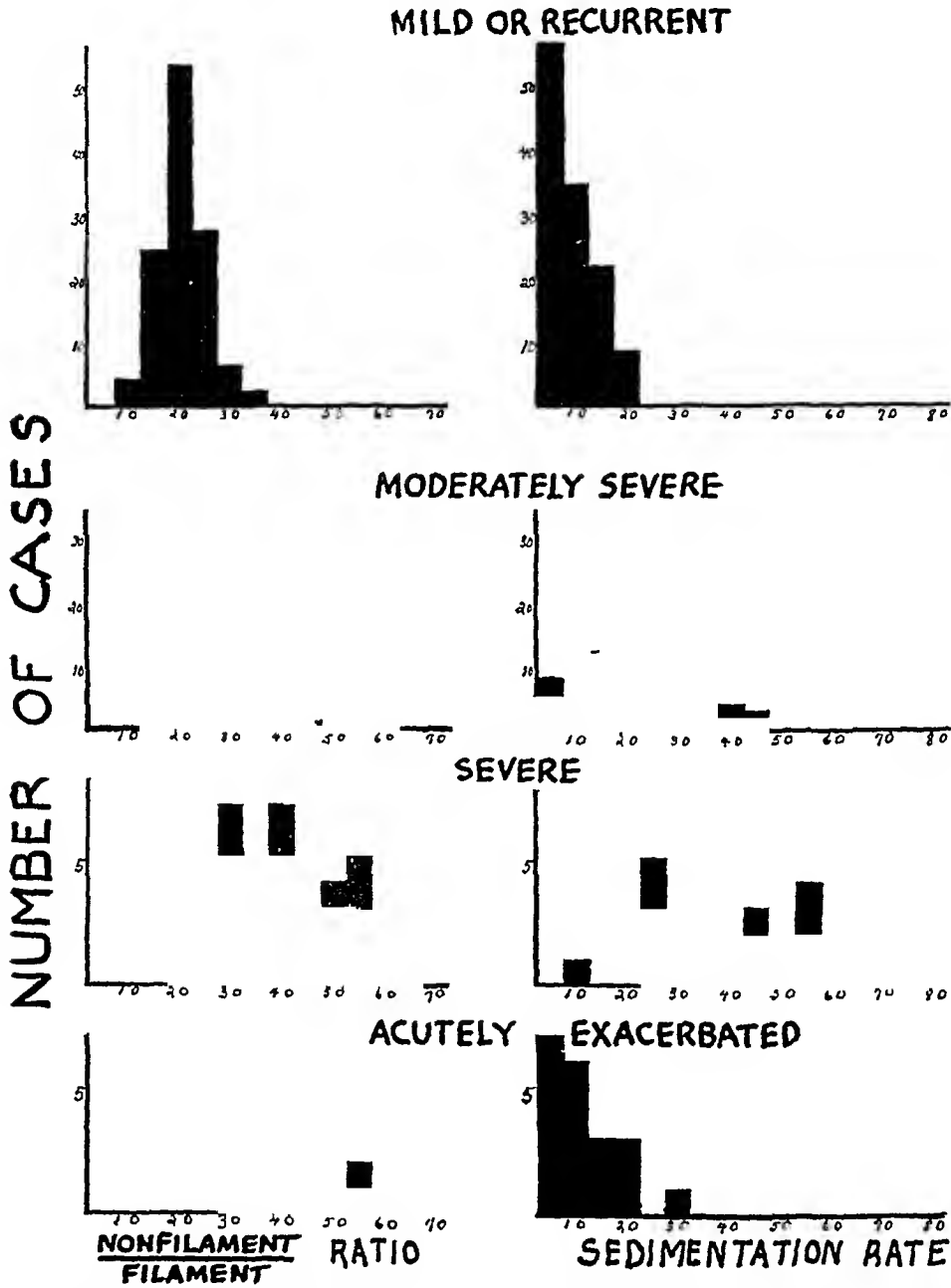


Chart 5—Nonfilament-filament ratios and sedimentation rates distributed according to severity of symptoms

tions from the general averages, but in no group was the number of cases sufficiently large or the deviation great enough to justify making positive inferences. In cases of oral infection (chart 4) the mean non-

filament-filament ratio was less than the mean for all cases by 4.31 times the standard error, but there was no significant variation in the sedimentation rate. In cases of colitis (chart 3) the mean nonfilament-filament ratio was 31.38, the difference from the mean of the entire series being 3.68 times the standard error, but again there was no significant difference in the sedimentation rate. In cases of duodenal ulcer (chart 4) the mean sedimentation rate was lowest (8.98 mm), the difference from the mean for all cases being 4.32 times its standard error. The mean nonfilament-filament ratio was 22.16, the difference from the general mean being 1.93 times its standard error.

In cases of rheumatoid arthritis (chart 4) there were significant increases. The mean nonfilament-filament ratio was 36.93, the difference from the general mean being 5.23 times its standard error. The mean sedimentation rate was 37.33 mm, the difference from the general mean being 9.1 times the standard error.

When the findings were distributed according to severity of symptoms (chart 5) significant differences were found. When symptoms were mild or recurrent the mean nonfilament-filament ratio was 18.56 (116 cases) and the mean sedimentation rate 7.2 mm (119 cases). When symptoms were of moderate severity the mean nonfilament-filament ratio was 24.22 (98 cases) and the mean sedimentation rate 19.99 mm (88 cases). When symptoms were severe the mean nonfilament-filament ratio was 40.1 (36 cases) and the mean sedimentation rate 39.91 mm (34 cases). In an additional 20 cases the symptoms at the time of examination were more or less acutely exacerbated. In these cases the mean nonfilament-filament ratio was 44 and the mean sedimentation rate 9.5 mm.

#### COMMENT

The values which have been used as normal standards for the nuclear count and the sedimentation rate vary considerably. Schilling's<sup>19</sup> values for the nuclear count, 64 per cent segmented neutrophils and 4 per cent young forms, which have been widely used, e.g., by Crocker and Valentine,<sup>20</sup> in their extensive studies, and by Nicolle,<sup>21</sup> Black,<sup>22</sup> Gorsky,<sup>23</sup>

19 Schilling, V. *The Blood Picture and Its Clinical Significance*, St. Louis, C. V. Mosby Company, 1929.

20 Crocker, W. J., Valentine, E. H., and Brody, W. Hemography-Controlled Nonspecific Immunotransfusions in the Treatment of Septicemia and Other Acute Infections, *J. Lab. & Clin. Med.* **20**:482 (Feb.) 1935. Crocker and Valentine (footnotes 7 and 10).

21 Nicolle, H. J. *The Schilling Index*, New Orleans M. & S. J. **84**:114 (Aug.) 1931.

22 Black, W. C. Schilling's Differential Count, *Colorado Med.* **27**:189 (June) 1930.

23 Gorsky, S. Interpretation of the Leucocyte Differential Count and the Schilling Nuclear Shift in the Blood, *M. J. & Rec.* **135**:468 (May 18) 1932.



Short and associates,<sup>24</sup> Finney and Dunlop,<sup>25</sup> Niehaus<sup>26</sup> and Steinberg,<sup>27</sup> are consistent with the results of Osgood's<sup>28</sup> recent studies on normal subjects. Further, Schilling's value for young forms is only slightly less than Cooke and Ponder's<sup>29</sup> value for their class I cells (nonfilamented), and his value for segmented cells approximates that for Cooke and Ponder's combined classes II, III, IV and V (filamented), provided Cooke and Ponder's values are expressed in percentages of the total leukocyte count. In the present study Schilling's values were used, which means that any nonfilament-filament ratio over 7 was considered abnormal. On this basis all the patients for whom counts were made had abnormal ratios, which is in agreement with Griffith's<sup>6</sup> findings in cases of focal infection.

In regard to the sedimentation rate, Westergren<sup>30</sup> called values up to 3 mm normal and values from 4 to 6 mm doubtful. Beaumont and Maycock,<sup>31</sup> Kilduffe,<sup>32</sup> Schulten<sup>3</sup> and Hirsh<sup>33</sup> mentioned similar normal standards, although all except Beaumont and Maycock gave a higher normal value for females than for males. In the present study Kilduffe's normal values of 3 mm for males and 5 mm for females were adopted as standards. By these standards 87 per cent of the males and 82 per cent of the females had rates above normal.

Thus it appears that the sedimentation rate is not as sensitive an indicator of minor variations in health as is the nonfilament-filament ratio, which showed abnormal values for all patients. Of patients with mild symptoms, 34 per cent had normal sedimentation rates (4 mm being used as the normal limit when rates were not distributed according

24 Short, C L, Dienes, L, and Bauer, W. Rheumatoid Arthritis. A Comparative Evaluation of the Commonly Employed Diagnostic Tests, *J A M A* **108** 2087 (June 19) 1937.

25 Finney, R H, and Dunlop, J N. The Schilling Blood Count, *Colorado Med* **30** 212 (June) 1933.

26 Niehaus, F W. Value of Leucocyte Counts According to Arneith-Schilling Formula in Clinical Medicine, *M Clin North America* **12** 395 (Sept) 1928.

27 Steinberg, C L. The Schilling Count in Fifty-Nine Cases of Rheumatoid Arthritis, *Am J M Sc* **190** 98 (July) 1935.

28 Osgood, E E. Normal Hematologic Standards, *Arch Int Med* **56** 849 (Nov) 1935.

29 Cooke, W E, and Ponder, E. The Polynuclear Count, Philadelphia, J B Lippincott Company, 1927.

30 Westergren, A. On the Stabilitary Reaction of the Blood in Pulmonary Tuberculosis, *Brit J Tuberc* **15** 72 (April) 1921.

31 Beaumont, G E, and Maycock, J W. The Erythrocyte Sedimentation Rate, *Lancet* **2** 19 (July 6) 1935.

32 Kilduffe, R A. The Clinical Interpretation of Blood Examinations, Philadelphia, Lea & Febiger, 1931, p 115.

33 Hirsh, J E. The Value of the Sedimentation Test as a Diagnostic Aid, *Ann Int Med* **10** 495 (Oct) 1936.

to sex), but only 1 had a nonfilament-filament ratio below 10. When the symptoms were moderate, 6 per cent of the patients had normal sedimentation rates, while the lowest nonfilament-filament ratio was 12. When the symptoms were severe there were no normal observations, the lowest sedimentation rate being 9 mm and the lowest nonfilament-filament ratio 18. When symptoms were acutely increased the nonfilament-filament ratio was elevated to a much greater extent than the sedimentation rate. The greater sensitiveness of the nonfilament-filament ratio in arthritis has been commented on by Steinberg<sup>27</sup> and in tuberculosis by Leitner<sup>34</sup> and Thiele<sup>35</sup>.

While the nonfilament-filament ratio is the more prompt indicator of changes in the activity of a disease process, it is generally agreed that the sedimentation rate tells more regarding fundamental changes in disease.<sup>36</sup> When remission occurs in a chronic infection the nonfilament-filament ratio falls, but the sedimentation rate remains elevated for a considerable time, a warning that body conditions have not returned to normal. In view of the readiness with which the nonfilament-filament ratio responds to acute exacerbations, it appears that an increased sedimentation rate would have greater significance in the diagnosis of chronic infection than would an increased nonfilament-filament ratio. For example, Sjogren<sup>5</sup> found the sedimentation rate more useful than the white blood cell count in the diagnosis of latent ocular infection.

The difference in sedimentation rate between the sexes was chiefly in values lying between the normal limits and 30 mm. Approximately equal percentages of males and females had normal rates or rates above 30 mm. When the abnormal rates under 30 mm were analyzed, the mean for females was 15.28 mm and the mean for males 10.7 mm. While the numerical difference between these means is no greater than that when all cases were included, the significance is greater (3.72 times the standard error).

When the findings were grouped according to age, the 21 to 30 year group showed a low sedimentation rate (9.1 mm), probably due not to any factor associated with age but to the fact that in this particular group there was a high percentage of cases in which the symptoms were mild. The high mean sedimentation rate found in the group of patients over 60 may have been due partly to the effect of age but was apparently

34 Leitner, J. Significance of White Blood Picture in Its Relationship to Sedimentation Speed of Erythrocytes in Clinical Evaluation of Some Forms of Pulmonary Tuberculosis, *Beitr z Klin d Tuberk* 86 297 (June 25) 1935.

35 Thiele, G. Significance of White Blood Picture in Relation to Sedimentation Speed of Erythrocytes in Clinical Estimation of Some Forms of Pulmonary Tuberculosis, *Beitr z Klin d Tuberk* 86 126 (March 23) 1935.

36 Blood Sedimentation Tests, Queries and Minor Notes, *J A M A* 108 577 (Feb 13) 1937.

due chiefly to the presence in this group of an unusually high number of patients with severe symptoms

When grouped according to the diagnosis, the findings in only a few diseases showed significant differences from the general averages. In colitis the mean nonfilament-filament ratio was significantly above the general average, although the mean sedimentation rate was not affected. The figures reported here are much lower than those reported by Garvin and Borgen<sup>1</sup> in cases of ulcerative colitis, as would be expected in view of the fact that only a few cases of ulcerative colitis, in all of which the disease was quiescent, were included in the present series.

In cases of duodenal ulcer the mean sedimentation rate was significantly lower than the general average. This is in keeping with Schindler and Gnagi's<sup>4</sup> finding that the sedimentation rate is low in cases of uncomplicated peptic ulcer.

Patients with rheumatoid arthritis showed a mean nonfilament-filament ratio and mean sedimentation rate significantly above the general averages. The mean sedimentation rate was not as high as that reported by Bannick and his associates<sup>15a</sup> (71.6 mm), but was close to that reported by Rawls and his associates<sup>37</sup> and by Forestier<sup>38</sup>. A considerable variation in the means reported by various authors might be explained by differences in the severity of the disease. The increase in the nonfilament-filament ratio is in general agreement with the increased nonfilamented cell counts reported in cases of rheumatoid arthritis by Steinberg,<sup>27</sup> Hartung and his associates,<sup>39</sup> Steinbrocker and Hartung<sup>40</sup> and Rawls and his associates,<sup>37</sup> although the mean nonfilamented cell counts reported by Steinbrocker and Hartung<sup>40</sup> and by Hartung and his co-workers<sup>39</sup> were relatively higher than the mean of the present series.

The mean sedimentation rate in "rheumatism" was somewhat higher than that reported by Bannick and his associates<sup>15a</sup> in fibrositis (11.6 mm) and did not agree with Schulten's<sup>3</sup> finding of a "normal" sedimentation rate in muscular rheumatism.

In general, detailed study of the cases reported gave the impression that the sedimentation rate and the nonfilament-filament ratio varied primarily with the severity of symptoms, rather than with the type of disease. For example, patient 93, with quiescent rheumatoid arthritis,

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37 Rawls, W. B., Gruskin, B. J., Ressa, A. A., and Jordan, M. The Sedimentation Rate and Polymorphonuclear Count in Rheumatoid and Mixed Arthritis, *J. Lab. & Clin. Med.* **19**: 830 (May) 1934.

38 Forestier, J. The Treatment of Rheumatoid Arthritis with Gold Salts Injections, *Lancet* **1**: 441 (Feb. 27) 1932.

39 Hartung, E. F., Davis, J. S., Steinbrocker, O., and Straub, M. E. The Blood in Arthritis, *J. A. M. A.* **106**: 1448 (April 25) 1936.

40 Steinbrocker, O., and Hartung, E. F. The Filament-Nonfilament Count in Chronic Arthritis, *J. A. M. A.* **100**: 654 (March 4) 1933.

had a sedimentation rate of 13 mm and a nonfilament-filament ratio of 20, while patient 263, with chronic sinusitis and "rheumatism," had a sedimentation rate of 51 mm and a nonfilament-filament ratio of 30

These observations add confirmation to the many reports which have endorsed the earlier findings by Westergren,<sup>30</sup> Schilling<sup>19</sup> and Cooke and Ponder<sup>29</sup> that the sedimentation rate and the polymorphonuclear count are useful in determining the severity of disease, in following its progress and in judging the value of treatment

#### SUMMARY

Observations on the sedimentation rate and nuclear count were made on 292 patients with chronic or frequently recurring symptoms which were suspected of being secondary to low grade chronic infection. Of this number 277 showed evidence of either chronic sinusitis or chronic nasopharyngitis. There were 52 patients with chronic bronchitis, 75 with symptoms referable to the biliary tract, 78 with gastrointestinal conditions, 36 with symptoms referable to the urinary tract, 40 with arthritis and 36 with "rheumatism."

The mean sedimentation rate (Westergren) for all patients was 15.9 mm; the mean nonfilament-filament ratio ( $\frac{\text{nonfilamented neutrophils} \times 100}{\text{filamented neutrophils}}$ ) was 25.2. The mean sedimentation rate for females was higher than that for males, but there was no variation in the nonfilament-filament ratio. There were no significant variations when the sedimentation rates and nonfilament-filament ratios were distributed according to age, except for a possibly significant increased sedimentation rate in the group of patients over 60. When the findings were distributed according to disease there were only questionable variations, except for colitis (high nonfilament-filament ratio), duodenal ulcer (low sedimentation rate) and rheumatoid arthritis (high sedimentation rate and nonfilament-filament ratio).

When the findings were distributed according to severity of symptoms, there was a direct relationship. As symptoms increased the sedimentation rate and nonfilament-filament ratio increased. When symptoms were more or less acutely exacerbated the nonfilament-filament ratio was high, but the sedimentation rate was relatively low.

According to Schilling's, Cooke and Ponder's or Osgood's criteria for normal neutrophilic distribution, the nonfilament-filament ratio was increased above normal in practically all cases. According to Kilduffe's normal limits of 3 mm for males and 5 mm for females, more than 80 per cent of the sedimentation rates observed were abnormal.

On the basis of these findings, the nonfilament-filament ratio appears to be a more sensitive indicator of the presence of disease than the sedimentation rate, although the readiness of its response to acute exacer-

bation makes the finding of an increased sedimentation rate of more significance in the diagnosis of chronic illness than the finding of an increased nonfilament-filament ratio

#### CONCLUSIONS

Practically all of a group of 292 patients with symptoms of low grade chronic disease showed an increase in the nonfilament-filament ratio, while more than 80 per cent showed an increased sedimentation rate

The sedimentation rate and nonfilament-filament ratio showed only minor variations when distributed according to age, sex or diagnosis. When distributed according to the intensity of symptoms they showed a direct relationship to increases in the severity of illness.

These findings should prove useful in following the course of low grade chronic disease and in evaluating treatment.

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# EVALUATION OF THE CONCENTRATION OF SERUM SULFATE

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In 1931 we<sup>1</sup> recorded data on the concentration of serum sulfate and of blood urea in cases of renal insufficiency of varying degrees. At that time we stated specifically that the concentration of serum sulfate may be increased in a case of early renal insufficiency while the concentration of blood urea is within normal limits. However, we now believe this fact may be more precisely stated by saying that the concentration of serum sulfate may exceed the normal limits in cases of mild, rather than early, renal insufficiency. When there is definite renal insufficiency, the concentrations of both blood urea and serum sulfate will usually be increased. Why the value for serum sulfate is increased when the concentration of blood urea is normal is a phenomenon we cannot explain. The functional activity of the kidney is so complex, however, that a moderate increase of any one substance in the serum or blood should not be used implicitly as an index of the functional ability of this organ. In fact, clinical experience has proved that physicians should not depend too greatly on prognostic data that are obtained from the most comprehensive tests of renal function. Any test of renal function at times may indicate good kidneys, and yet the patient, if subjected to a serious operation, may succumb to renal failure immediately afterward.

Determination whether the concentration of serum sulfate can be used as an index of renal function was not the object of this study, which was rather to find out more about the frequency with which increased concentrations of serum sulfate occur in cases of mild renal insufficiency. The relation that the increase in concentration of serum sulfate has to the decrease in the values obtained by the urea clearance test, to the increase in the concentration of blood urea and to the specific gravity of the urine was our chief concern.

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1 Wakefield, E G, Power, M H, and Keith, N M. Inorganic Sulfates in the Serum in Early Renal Insufficiency. Significance of Determinations, J A M A 97 913-917 (Sept 26) 1931

The method used in determining the concentration of serum sulfate was a modification of Cope's<sup>2</sup> procedure, namely, alkalimetric titration of benzidine sulfate separated from trichloroacetic acid filtrates of serum by means of a solution of benzidine in acetone. The technic has been used by us for several years.<sup>3</sup> In our hands the values obtained by this method for the inorganic sulfate in normal serum have been, as might be expected, somewhat lower than the results of our earlier analyses, in which the benzidine sulfate was oxidized with potassium bichromate. Recently we have found that the use of alcohol in the precipitation of benzidine sulfate from a trichloroacetic acid filtrate is more satisfactory than the use of acetone, although the results obtained by the two methods of precipitation are not greatly divergent and are in reasonable agreement with the results of determinations by the microgravimetric barium sulfate method. A report of our experience with these and other methods for the determination of the concentration of inorganic sulfate in serum has recently been published.<sup>4</sup>

Øllgaard<sup>5</sup> has recently developed a procedure in which the sulfate in precipitates separated from trichloroacetic acid filtrates by benzidine in acetone is titrated with a solution of barium chloride, in the presence of sodium rhodizonate as an indicator. This procedure may possibly be somewhat more specific for sulfate than the alkalimetric titration. The values for serum sulfate obtained by its use, however, appear to be in close agreement with those obtained in this study.

The range of normal values for the concentration of sulfate in the serum was obtained by a study of 125 normal persons, the criteria for their selection being as follows: (1) the clinical absence of evidence of organic disease history and general physical examination, (2) absence of albumin, sugar, casts, pus and blood in the urine, (3) a concentration of blood urea of less than 40 mg per hundred cubic centimeters, and (4) normal or decreased urea clearance (determined in about half the cases).

The mean value was 3.7 mg of sulfate (1.23 mg of sulfur) in 100 cc of serum, and 95 per cent of the values fell within the range of

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2 Cope, C. L. Determination of Inorganic Sulfate in Human Blood-Plasma by Micro-Titration, *Biochem J* **25** 1183-1189, 1931

3 Power, M. H., Wakefield, E. G., and Peterson, R. D. The Micro-determination of Ethereal Sulfate in Blood Serum, *J Biol Chem* **105** 13711-13711 (May) 1934

4 Power, M. H., and Wakefield, E. G. A Volumetric Benzidine Method for the Determination of Inorganic and Ethereal Sulfate in Serum, *J Biol Chem* **123** 665-678 (April) 1938

5 Øllgaard, E. Undersøgelser blodets vandopløselige svovlforbindelser, Thesis, Copenhagen, Nyt Nordisk Forlag Arnold Busck, 1937, Eine mikro-titrimetrische Methode zur Bestimmung von Sulfaten im Plasma, *Biochem Ztschr* **274** 181 (Nov 14) 1934

2.4 to 4.9 mg of sulfate (0.80 to 1.63 mg of sulfur) per hundred cubic centimeters of serum

In order to obtain proper data, it was necessary to designate certain arbitrary limits of what was to constitute the "normal" and, conversely, the "abnormal." In using the urea clearance test, we therefore chose to designate all values of less than 40 (the number of cubic centimeters of blood cleared of urea per minute when the volume of urine excreted was less than 2 cc per minute) as below normal, or decreased. All maximum values of less than 60 were considered as indicating a decreased clearance. When the average excretion of urine was less than 0.5 cc per minute the data were not included. It seemed well to limit further

TABLE 1—*Relation of Urea Clearance and the Concentration of Serum Sulfate to the Concentration of Blood Urea*

Blood Urea	Serum Sulfate				Urea Clearance			
	Increased		Normal		Decreased		Normal	
	Cases	Per-centage	Cases	Per-centage	Cases	Per-centage	Cases	Per-centage
Increased (143 cases)	113	79	30	21	118	82.5	25	17.5
Normal (503 cases)	85	16.7	423	83.3	147	23.9	361	71.1

TABLE 2—*Relation of Urea Clearance and the Concentration of Blood Urea to the Concentration of Serum Sulfate*

Serum Sulfate	Blood Urea				Urea Clearance			
	Increased		Normal		Decreased		Normal	
	Cases	Per-centage	Cases	Per-centage	Cases	Per-centage	Cases	Per-centage
Increased (193 cases)	113	57	85	43	141	71.2	57	28.8
Normal (453 cases)	30	6.6	423	93.4	124	27.4	329	72.6

the group of patients to be studied by omitting all those whose concentration of urea was more than 100 mg per hundred cubic centimeters of blood. Concentrations of 44 mg or more of urea in 100 cc of blood were considered increased. Concentrations of 5 mg or more of sulfate (1.67 mg or more of sulfur) in each 100 cc of serum were considered to be increased.

In tables 1 and 2 are recorded the data obtained from a study of 651 hospital patients who were known to have or were suspected of having renal insufficiency. There were no set clinical criteria for studying these patients except that the obtaining of further data on renal function was indicated. On the morning of the tests the patient was kept in bed. The urea clearance test was performed in duplicate periods. As indicated in table 1, the concentration of blood urea was



increased in 143 cases and was normal in 508 cases. The values for serum sulfate were increased in 79 per cent and normal in 21 per cent of the cases in which the concentration of blood urea was increased and increased in 16.7 per cent of the 508 cases in which the concentration of blood urea was normal. It is this 16.7 per cent of cases in which the concentration of serum sulfate was increased that has been of interest to us. We believe that this series is large enough to corroborate our original contention that an increased concentration of serum sulfate may occur while the concentration of blood urea remains within normal limits. That mild renal insufficiency was present in some of the 16.7 per cent of cases was proved by the subsequent course. The decrease in the clearance of urea and the increase in the concentration of serum sulfate did not always parallel each other. This fact is demonstrated in tables 1 and 2, which show that increased concentrations of serum sulfate occurred in 198 of the 651 cases and that a decreased clearance of urea occurred in only 141, or 71.2 per cent of the 198 cases. Whereas the clearance of urea was decreased in 27.4 per cent of cases in which the concentration of serum sulfate was normal, it was not altered in 28.8 per cent of the cases in which the concentration was increased.

The urea clearance test, when properly employed as a test of renal function, is repeated at intervals, it is the general trend of the results of any test which indicates its prognostic significance. This fact also should be true of the concentration of blood urea or the specific gravity of the urine when they are used as indicators of renal function. In our practice it is not practical, and is often not possible, to employ the urea clearance test in this way. However, in cases of nephritis in which increasing azotemia and a decrease in the concentration of hemoglobin occur the test alone often furnishes a satisfactory prognosis.

We believe with many other observers that in the absence of large amounts of albumin in the urine (grade 2 or less, on a basis of 4) the specific gravity of the urine is an excellent indicator of renal function. Under most circumstances, when the renal lesion is not acute, as it is in acute glomerulonephritis, kidneys which excrete urine of a specific gravity of 1.025 or more may be considered good. Tables 3 and 4 contain data obtained in 100 cases under circumstances similar to those observed in tables 1 and 2 except that in all the cases in tables 3 and 4 the specific gravity of a twelve hour specimen of urine was 1.025 or greater. To check the increased concentration of serum sulfate and the urea clearance against the specific gravity of a twelve hour specimen of urine when this was 1.025 or more would furnish some idea of the probable influence of a low intake of fluid on the results of the tests. It will be seen that an increased concentration of blood urea occurred

in 41 of the 100 cases. In all these cases the values were less than 60 mg per hundred cubic centimeters. The concentration of serum sulfate was increased in 25 cases and normal in 75 cases. In 51.2 per cent of cases in which the blood urea was increased the serum sulfate also was increased. In 84 per cent of cases in which the concentration of serum sulfate was increased the concentration of blood urea also was increased. The results obtained with the urea clearance test indicated the same general trend, in 56 per cent of cases in which the blood urea was increased, the urea clearance was decreased. When the data obtained for the 100 patients in tables 3 and 4 are separated on the

TABLE 3—*Relation of Urea Clearance and the Concentration of Serum Sulfate to the Concentration of Blood Urea in 100 Cases in Which the Specific Gravity of the Urine was 1.025 or Higher*

Blood Urea	Serum Sulfate				Urea Clearance			
	Increased		Normal		Decreased		Normal	
	Cases	Per-centage	Cases	Per-centage	Cases	Per-centage	Cases	Per-centage
Increased (41 cases)	21	51.2	20	48.8	23	56	18	44
Normal (59 cases)	4	6.8	55	93.2	46	78	13	22

TABLE 4—*Relation of Urea Clearance and the Concentration of Blood Urea to the Concentration of Serum Sulfate in 100 Cases in Which the Specific Gravity of the Urine was 1.025 or Higher*

Serum Sulfate	Blood Urea				Urea Clearance			
	Increased		Normal		Decreased		Normal	
	Cases	Per-centage	Cases	Per-centage	Cases	Per-centage	Cases	Per-centage
Increased (25 cases)	21	84	4	16	18	72	7	28
Normal (75 cases)	20	26.6	55	73.3	51	68	21	32

basis of increased or decreased values for the concentration of serum sulfate, it is found that in 84 per cent of cases in which the concentration was increased the blood urea also was increased. The urea clearance was decreased in 72 per cent of cases in which the serum sulfate was increased. In brief, these data indicate that a low fluid intake seems more readily to affect the concentration of blood urea than it does the urea clearance or the concentration of serum sulfate.

That a low fluid intake does not readily affect the concentration of serum sulfate has been demonstrated by study of the concentrations of this substance in cases in which urinary obstruction was produced by hypertrophy of the prostate gland and cases of pyloric obstruction associated with dehydration. In such cases the concentration of urea

may reach 100 mg per hundred cubic centimeters of blood while the concentration of serum sulfate remains normal

In our experience, gained by determining the concentration of serum sulfate in cases of known and suspected renal insufficiency, the conclusion that an increased concentration of sulfate is associated with failure of renal function is reasonable. The concentration of serum sulfate may be increased in renal insufficiency when that of blood urea is normal. This study illustrates that when the patient has definite renal insufficiency all the tests of so-called renal function will indicate its presence. However, if there is uncertainty as to the status of renal function, the results obtained with any one functional test may vary greatly if the test is repeated often. Therefore, if a number of these tests are conducted synchronously, as has been done in this study, variations in the results are to be expected.

In a report which we made in 1931 on the concentration of sulfate in the serum we said that it had been observed to reach unpredictable heights. Since 1931 we have repeatedly confirmed this observation. In 1 case in which the concentration was high we were able to check the results obtained with the titration method by using the gravimetric method to determine the amount of sulfate in the filtrate of 50 cc of serum. In several cases in which the concentration of serum sulfate was high studies of the acid base equilibrium have been made in order to check our method of determining the concentration of sulfate in the serum. For instance, in 1 case the concentration of sulfate was 162 milliequivalents per liter of serum. The concentration of total determined acids plus base protinate was 146.3 milliequivalents per liter of serum (chlorides 95.7, bicarbonate 11.2, phosphates 6.9, sulfate 16.2, lactic acid 0.6 and base protinate 15.7), and the concentration of total base was 151.4 milliequivalents per liter of serum (sodium, 140, potassium, 6, calcium, 3.1, and magnesium, 2.3). A concentration of 20 milliequivalents of sulfate per liter of serum can and actually does occur, when it does, the patient suffers from uremic acidosis and has been suffering from nausea and vomiting for days, usually for a fortnight. There may be a marked decrease in the concentration of chlorides in the plasma and in the carbon dioxide-combining power of the plasma.

#### SUMMARY

Ninety-five per cent of the values for the concentration of serum sulfate in normal persons ranged from 2.4 to 5 mg (0.8 to 1.67 mg of sulfur) per hundred cubic centimeters. It was increased for 16.7 per cent of patients suspected of having mild renal insufficiency, while the concentration of blood urea was within normal limits. The blood urea was increased for 6.6 per cent of patients who had normal concentra-

tions of serum sulfate, an association seemingly related to low intake of fluid and, according to present data, a favorable prognostic indication. Urea clearance tests, when performed under the conditions described in this study, vary widely. In so-called uremic acidosis, concentrations of serum sulfate may reach unpredictable heights. We have observed concentrations of 20 miliequivalents in cases in which the concentration of chlorides and the carbon dioxide-combining power of the plasma were reduced.

# MASCUINOVOBLASTOMA

## PRIMARY MASCULINIZING TUMOR OF THE OVARY (SO-CALLED LARGE CELL VARIETY—HYPERNEPHROID—LUTEOMA)

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Two nonrelated ovarian tumors associated with masculinization are now described, the arrhenoblastoma and a large cell type variously called hypernephroma, hypernephroid and luteoma. The reason for the variety of names for the latter growth is the imperfect knowledge of its histogenesis, some authors favoring its origin from an adrenal rest and others from lutein elements. The first report to appear in the literature was that of Bovin<sup>1</sup>. Glynn<sup>2</sup> in 1917 criticized inclusion of the tumor among ovarian growths, on the ground that it lay in the broad ligament and not primarily in the ovary.

Other reports of growths at first included in this group but later discarded followed. Thus Tuffier<sup>3</sup> reported a case in which the diagnosis was primary adrenal tumor with metastasis to the ovary, while Cosacesco and his associates<sup>4</sup> classified the lesion as *lutérome*. However, the presence of large bilateral adrenal masses as well as the ovarian growth renders the case unacceptable. Buttner<sup>5</sup> described a tumor composed of tubules and lipoid-containing cells, a combination representing, as he concluded, a transition form between the arrhenoblastoma and the so-called hypernephroid. Meyer<sup>6</sup> expressed the belief that it should be

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From St Vincent's Hospital

1 Bovin, E. Ueber im weiblichen Genitale primär entstandene hypernephroide Geschwülste, Nord med Ark **15** 1, 1908, Des tumeurs hypernephroïdes primitives des organes génitaux féminins, Semaine med **30** 66, 1910

2 Glynn, E. A Comparison Between Ovarian "Hypernephroma" and Luteoma and Suprarenal Hypernephroma, with Comments on Suprarenal Virilism, J Obst & Gynaec Brit Emp **28** 24, 1921

3 Tuffier, C. La virilisme surrenal, Bull Acad de med, Paris **30** 726, 1910

4 Cosacesco, A., Draganescu, S., Georgescu, M., and Dinischiotu, G. T. Lutérome de l'ovaire. Contribution anatomo-clinique à l'étude du virilisme ovarien, Presse méd **68** 1264, 1931

5 Buttner, A. Ueber Eierstockgeschwülste mit Vermännlichung, Virchows Arch f path Anat **287** 452, 1932

6 Meyer, R., cited by Benecke, E. Zur Frage der Vermännlichungsgeschwülste des Eierstockes nebst Mitteilung von zwei neuen Fällen, Virchows Arch f path anat **294** 38, 1934

classified in the latter group, while Schiller<sup>7</sup> stated that the presence of tubules placed it in the former. The case reported by Parhon and Aburel<sup>8</sup> has likewise been discarded, on the ground that the ovarian tumor was multicystic and further that there was insufficient evidence to warrant classifying it in any particular group. Thus when Novak and Wallis<sup>9</sup> added their report, there were only 3 acceptable cases (those of Cosacresco and his associates,<sup>4</sup> Sellheim<sup>10</sup> and Bingel<sup>11</sup>), theirs making a fourth. Since then Saphir and Parker<sup>12</sup> and Maxwell<sup>13</sup> have published reports of cases. Saphir and Parker called the lesion in their case an example of adenal rest in the ovary and concluded that it was different from the tumor in question. Yet, aside from size, we could see no microscopic differences between it and the others referred to. Maxwell<sup>13</sup> reported her case as an instance of arrhenoblastoma. Schiller<sup>14</sup> expressed the opinion that it belonged to the so-called hypernephroid group instead.

#### REVIEW OF CASES REPORTED IN THE LITERATURE

**BOVIN'S<sup>1</sup> CASE**—The patient, a 28 year old woman, first came under observation in September 1907. At the age of 21 there had been cessation of menstrual periods, accompanied a year later by hirsutism, which gradually became pronounced until she found it necessary to shave regularly. Further, there was persistent abdominal pain, gradually becoming worse.

On physical examination she appeared to be well built and had an abundant growth of hair about the face and abdomen. Development of the breasts was normal. On vaginal examination a movable mass, about the size of a fist, was felt to the left of and behind the uterus. The right side appeared normal.

At operation, in March 1908, a nonpedunculated tumor was found on the left side, in the pouch of Douglas. The fallopian tube lay free on its upper surface. The right ovary was small and sclerotic.

Two and one-half months postoperatively the menstrual periods returned and recurred regularly thereafter. At the last notation, on Aug 9, 1909, one and

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<sup>7</sup> Schiller, W., cited by Novak and Wallis<sup>9</sup>

<sup>8</sup> Parhon and Aburel, cited by Cosacresco, Draganescu, Georgescu and Dimischiotu<sup>4</sup>

<sup>9</sup> Novak, J., and Wallis, O. Vermännlichung und Wiederverweiblichung (Beitrag zur Kenntnis der "Luteinzellentumoren" des Ovariums), Arch f Gynak **164** 543, 1937

<sup>10</sup> Sellheim, H. Vermännlichung und Wiederverweiblichung bei einem ausgewachsenen Individuum, Ztschr f mikr-anat Forsch **3** 382, 1925

<sup>11</sup> Bingel, A. Verschwinden von Polycythämie und Rückbildung von Vermännlichung nach Entfernung eines Luteinzellentumors, Deutsche med Wchnsch **50** 330, 1924

<sup>12</sup> Saphir, W., and Parker, M. L. Adrenal Virilism, J A M A **107** 1286 (Oct 17) 1936

<sup>13</sup> Maxwell, A. F. Masculinizing Tumors of the Ovary, West J Surg **45** 134, 1937

<sup>14</sup> Schiller, W., cited by Maxwell<sup>13</sup>

one-half years after operation, her periods had continued regularly and the hirsutism had disappeared. This patient, according to Bergstrand,<sup>15</sup> later became pregnant.

*Pathologic Report*—The specimen consisted of an irregularly round soft fluctuating growth, 8.5 by 8 by 6 cm, with a smooth lobulated surface, over one portion of which stretched a normal fallopian tube, while at another was attached a walnut-sized gray smooth spongy mass. On section the main portion of the specimen was composed of a lobulated growth, uniformly yellow and of brainlike consistency. The smaller nodule, which on section was grayish red, thinned out at its periphery to form a capsule about the main mass. On microscopic section the yellow tumor was composed largely of either round or polyhedral cells, measuring 30 to 35 microns, with distinct outlines and filled with fat and a finely granular cytoplasm. Other cells were present in which the granular cytoplasm was more abundant, stained darker and contained no vacuoles of fat. The supporting stroma consisted of a small amount of connective tissue accompanying the treelike course of the blood vessels. Tumor cells filled the spaces between the vascular branches. Regressive changes were noted, such as cells undergoing atrophy and replacement fibrosis. The walnut-sized mass consisted of ovarian tissue.

BINGEL'S <sup>11</sup> CASE—A 47 year old farmer's wife, who had married at 22, had given birth to 4 children. After the last pregnancy, at 29, her menstrual periods became irregular and remained so for five years, after which they stopped completely. At this time she suffered from headaches, the hair of the scalp fell out and she put on weight. Further, a beard and moustache appeared, so that at the age of 37 she had to shave daily. The voice changed, and she became cyanotic. Six years later polydipsia developed, the patient drinking 3 or 4 quarts (2,840 to 3,785 cc) a day. Her physical appearance at this time was masculine. The hair on the head was thin, while that over the entire body was plentiful, particularly on the chest and abdomen. She had a strong bony framework, with well developed muscles. There was abdominal obesity. A hard mass the size of a grapefruit was felt in the lower part of the abdomen. Laboratory tests showed sugar in the urine, a red blood cell count of 8,900,000 and 130 per cent hemoglobin.

She was operated on on Sept. 19, 1919, the uterus and both tubes and ovaries being removed.

*Pathologic Report*—An intramural fibromyoma the size of a grapefruit was present in the uterus. Whereas the left ovary appeared sclerotic, the right measured 9 by 9 by 4 cm. Section exposed a solid orange colored tumor surrounded by a capsule 3 to 4 mm thick.

On microscopic examination the tumor was seen to be composed of irregularly shaped cells with large vesicular nuclei containing distinct nucleoli. Cytoplasm was abundant, granular and eosinophilic. The cells were arranged in irregular groups and strands similar to those in corpus luteum. The stroma was scant. No fat was demonstrated in the tumor cells. The author suggested the name lutein cell tumor. The left ovary was sclerotic.

She was followed for three years after operation, by the end of which time she had completely regained her feminine habitus. The hair on the scalp had grown back, and that about the chest, neck and shoulders had disappeared. She still had to shave twice a week, however. The red blood cell count was 5,600,000.

SELLHEIM'S <sup>10</sup> CASE—The patient was a 49 year old woman who had been pregnant three times, one pregnancy resulting in miscarriage. Her menstrual

<sup>15</sup> Bergstrand, H. Ueber die Natur der virilisierenden Ovarialtumoren, Acta path et microbiol Scandinav, 1933, supp 16, pp 31-46.

periods began when she was 13 and ended abruptly at 43, the latter event having been associated with a gradual change of habitus to a coarse, masculine type. A heavy growth of hair appeared on the face and covered the entire body. At the same time the hair of the scalp began to fall out, the voice deepened and the larynx protruded.

Physical examination showed that the body was small, obese and coarse. She had a masculine face covered with beard and moustache. A dense growth of hair was present on the face, chest, abdomen, limbs and shoulders. The breasts were fatty, flat and pendulous. There was a penis-like clitoris, 4 cm long by 1.5 cm thick. A hard nodular mass filled the pelvis.

The operative procedure consisted in removing a large fibromyomatous uterus, together with both tubes and ovaries. The right ovary was small and sclerotic and the left of normal size. From the surface of the latter there protruded a chestnut-sized mass with a smooth surface.

Three weeks after the operation the beard grew lighter, the clitoris smaller and the voice softer. In ten months the clitoris was of normal size. At the end of a year all signs of masculinity had disappeared.

*Pathologic Report*—Immediately after removal the tumor appeared grayish red. Microscopically it was composed almost uniformly of one type of polygonal cell, measuring 7 to 16 microns, with a distinct outline and filled with an abundance of granular cytoplasm that was free of fat and glycogen. The nuclei were round or oval, measured 6 by 9 microns and had prominent nucleoli. Scattered here and there was an occasional cell, almost twice the usual size, with the same type of cytoplasm and nucleus. A vascularized connective tissue stroma radiated in from the capsule to divide the growth into cellular masses of different sizes. Various opinions were offered as to the nature of the growth. Several physicians, Berbingler, Marchand and Lubarsch, leaned toward a diagnosis of hypernephroma. Mathias suggested, in addition, corpus luteum tumor. Regardless of its nature, he stated that it belonged to the same class as those in the case of Bovin and that of Bingel.

*Case of Cosacesco and His Associates*<sup>4</sup>—A 34 year old woman complained of amenorrhea and masculinization of seven and five years' duration, respectively. Before this she had been perfectly normal. She had a lean masculine habitus. A dense growth of hair covered the face, chest, abdomen and extremities. In contrast, the frontal and parietal portions of the scalp were bald. The clitoris was large and the voice deep. *Per vaginam* an enlarged left ovary could be felt. Its removal initiated a dramatic reversal of symptoms. The menstrual flow appeared in thirty-two days and recurred regularly thereafter. Gradually her features and figure softened and the hirsutism disappeared, so that in two years she again appeared completely feminine.

*Pathologic Report*—The ovary was round, 5 cm in diameter and of cystic consistency. Section showed it to be a solid yellow nodule, encapsulated by a thin, firm fibrous coat, which microscopically was seen to be thinned ovary. The tumor was composed of cells of uniform size, filled with large quantities of lipid, and was richly vascular. From the fibrous capsule, bands of fibrous tissue ramified through the growth, dividing it into small cellular nests.

NOVAK AND WALLIS' CASE<sup>9</sup>—The patient was normal until 30 years of age, when amenorrhea developed, this was followed in a few months by headaches, deepening of the voice, a change to the masculine habitus and the development of hirsutism, with a beard which required daily shaving. Physical examination showed her to be muscular, with a male build and hair on the face, chest, abdomen



and extremities. The clitoris was large. She had a deep voice. The sugar content of the blood during fasting was 150 mg per hundred cubic centimeters. The red blood cell count was high, 6,600,000. The systolic blood pressure was 145.

At operation fluid was present in the abdomen, and the uterus and tubes were normal. Whereas the left ovary was small, the right was large, the size of a grapefruit.

*Pathologic Report*—The specimen weighed 390 Gm and measured 13.5 by 8 by 5 cm. Section showed one half to be composed of orange-colored tumor, with a gray, fibrous center. Independent but closely adjacent was a second nodule of similar nature. The remainder consisted of a grayish tissue—some portions compact and others more spongy because of contained blood vessels. Microscopically the nodules were composed of large, irregular polygonal cells, with a foamy cytoplasm rich in fat. The nuclei were large and in general vesicular. In the authors' opinion the tumor was of lutein cell origin, though they were not sure that it was not of adrenal origin.

One month after operation the periods returned and recurred regularly. Her habitus and voice gradually became softer, until at the end of two years she was completely feminized. The clitoris had become much smaller. Only the facial hairs were slightly heavier than normal, necessitating the use of a depilatory. The red blood cell count fell to 5,300,000 and the systolic blood pressure, from 145 preoperatively to 100 five months later. The blood sugar during fasting postoperatively was 115 mg per hundred cubic centimeters. Determinations before operation showed no estrogen, after operation 200 mouse units was present.

**SAPHIR AND PARKER'S<sup>12</sup> CASE**—The patient was a 15 year old girl with amenorrhea (for one year), hirsutism, obesity and deepening of the voice.

Physical examination showed obesity, confined to the trunk and face, and hypertrichosis of the cheeks, lips, chin, abdomen and chest. The mammae and clitoris were small, and the blood pressure was 110 to 130 systolic and 70 diastolic. Hormonal studies of the urine revealed an increase in estrogen and a decrease in the gonadotropic principle.

At operation the right ovary was seen to be slightly larger than its fellow. The right one was removed. Histologic examination showed a small, circumscribed nest of cells, with clear, vacuolated or finely granular eosinophilic cytoplasm. Both the cellular and the nuclear membranes were well defined. The authors felt that the nest of cells represented aberrant adrenal tissue.

Four days after operation a menstrual period occurred, and menstruation continued regularly for ten months (up to the date of the report). There was a slight loss of weight, but scarcely any change in the hypertrichosis. No vaginal cornification of the castrated mouse was obtained, even after an injection of 6 cc of urine within one hundred hours.

**MAXWELL'S<sup>13</sup> CASE**—The patient was a 62 year old woman with an uneventful endocrine history except for sterility. Five years after the menopause hirsutism developed, so that she had to shave daily.

On physical examination she presented a slender, muscular, masculine habitus. The hair covering the scalp was short and sparse, whereas that covering the face, chest, back, abdomen and limbs was luxuriant. The voice was deep and the clitoris enlarged. The blood pressure was 200 systolic and 100 diastolic. There were 6,100,000 red blood cells and 16 Gm of hemoglobin. The dextrose tolerance curve was abnormal, of diabetic type. Gonadotropic substances were absent from

the blood and urine. Estrogen was absent from the blood but present in the urine, up to 40 mouse units being excreted in twenty-four hours.

Both tubes and ovaries and the uterus were removed. The uterus contained many intramural fibroids. The right ovary was small and sclerotic. The left ovary was oval, measuring 4 by 2.5 by 1.5 cm.

Four months after operation the facial and bodily hirsutism had markedly decreased, the voice was softer, but the size of the clitoris had not diminished. A year later the breasts were larger and the figure had become more feminine. Hair had reappeared on the bald spots on the head and had practically disappeared over the body. She occasionally used a depilatory.

Dr. Maxwell sent us a slide containing a section from the left ovary, the description of which follows.

From the microscopic appearance of the slide the tumor must have been about the size of a pea. It occupied the medulla of the ovary and invaded slightly the cortex which encapsulated it. The tumor itself was composed of one type of cell, forming a diffuse, compact, richly cellular mass with no particular structure. The cells were slightly irregular in shape and size, averaging about 16 microns in diameter. A distinct cellular membrane was not visible. The cytoplasm was abundant, granular and eosinophilic. No clear cells were seen, so there was no suggestion of fat. Many cells contained coarse, brown granules. The nuclei were relatively large, round and oval, with granular chromatin material. In an occasional cell the nucleus was particularly large (up to 14 microns in diameter). Within the area occupied by the tumor cells were many blood vessels of varying size. In addition, there were many collapsed capillaries. The stroma was scant.

*Summary of Clinical Findings* (table 1) —The ages at which the patients came under observation ranged from 15 to 62 years, one to thirteen years after the onset of symptoms. In the youngest patient the onset occurred at 14 years, two years after the first menstrual period, in the oldest, at 50 years, five years after the menopause, and in others, at 21, 27, 30, 34 and 43 years. Neither sterility nor unusual fecundity appeared related to the syndrome, since 4 patients had from 1 to 4 children and only 1 was definitely sterile. When recorded, the establishment of menstruation, its continuance and its regular recurrence were normal. In every case except that (postmenopausal) reported by Maxwell, amenorrhea ushered in the syndrome. In 3 instances there was no antecedent disorder. In the others there were abnormalities such as irregular or diminished flow. Once established the amenorrhea was absolute, except in Sellheim's case, in which after eight years the patient suddenly began to bleed again. It is interesting that at about the time when there should have been a menstrual period one patient had recurrent headaches, mucous discharge and pain in the back.

After amenorrhea a train of other changes ensued, transforming the wholly feminine person into one with masculine characteristics, such as hirsutism, a deep voice, hypertrophy of the clitoris and a male habitus. These changes occurred either simultaneously with amenorrhea or developed at varying intervals, from six months to two years, except in Maxwell's patient, in whom they occurred five years after the meno-

pause Once initiated, the transformation proceeded inexorably until fully established within a year

The most conspicuous symptom was hirsutism This was characterized by a generalized increase of dense, coarse hair that would have done justice to any man It grew over the cheeks, chin, neck and lips at a rate necessitating daily shaving Further, it covered the chest, back, limbs and abdomen in true male fashion In contrast to the hypertrichosis of the body, in 4 cases the hair of the scalp proceeded to fall out, producing bald spots All patients had changes in voice In 3 the voice was described as deep or hoarse, while in the others it was still suffi-

TABLE 1—*Clinical Features of Cases Reported in the Literature\**

Case †	1	2	3	4	5	6	7
Age	34	28	49	15	47	32	62
Number of children	0	2	2	0	4	0	0
Age at onset of menstruation	—	—	13	12	—	12	16
Age at onset of amenorrhea	27	21	43	14	34	30	45
Age at onset of hirsutism	29	22	43	14	34	30	50
Loss of hair on scalp	Yes	—	Yes	No	Yes	Yes	Yes
Enlargement of clitoris	3.4 cm	—	4×1.5 cm	No	—	3.5 cm	Yes
Change in voice	Yes	—	Yes	Yes	Yes	Yes	Yes
Atrophy of breasts	Yes	No	Yes	Yes	—	Yes	Yes
Thyroid enlargement	—	—	—	—	Yes	Right lobe	Right lobe
Habitus	Male	—	Male	Female	Male	Male	Male
Headache	—	—	—	—	Yes	Yes	—
Loss of libido	Yes	—	Yes	—	No	Yes	—
Cyanosis	No	Yes	Yes	No	Yes	No	No
Weight	Thin	—	Obese	Obese	200 lb (90.7 Kg)	150 lb (72 Kg)	Thin
Erythrocyte count	—	—	—	—	8,900,000	6,600,000	6,100,000
Hemoglobin	—	—	—	—	130%	110%	—
Blood sugar	—	—	—	Normal	Increase	150	†
Blood pressure	—	—	—	110/70	120	145	220/100

\* Dashes indicate that no data were given

† The numbers in this and subsequent tables refer to the reports of the following authors (1) Cosaceseo and associates, (2) Bovin, (3) Sellheim, (4) Saphir and Parker, (5) Bingel, (6) Novak and Wallis and (7) Maxwell

‡ The dextrose tolerance test showed a curve characteristic of diabetes

ciently high pitched to be considered feminine The laryngeal cords were found enlarged in 2 instances and normal in 1, in the other cases there was no examination Further, in 1 case the larynx protruded externally, producing a so-called Adam's apple To complete the change, a male habitus developed in 5 instances, with some of the following features increase in musculature, widening of the shoulders, loss of female panniculus, development of veins on the arms, coarsening of the skin, angularity and coarse features and leanness The youngest patient retained her female figure but became obese, chiefly over the trunk, neck and face In 2 cases the habitus was not described Definite changes were noted in the breasts in every instance In some cases they diminished in size, becoming flat and atrophic, in others they became

flabby and pendulous. When the clitoris enlarged (in 4 cases) it did so to a marked degree, becoming in some instances penile in appearance. In 1 case there was no change, and in 2 its condition was not mentioned. Another interesting feature was the development in 3 patients of a livid complexion. This had its basis in polycythemia. Concerning the thyroid, of 4 cases in which its size was noted, it was normal in 1, in another the right lobe was enlarged, in a third the right lobe contained a calcific mass (the patient had symptoms of hyperthyroidism) and in the last there was general enlargement. Definite hypertension was present in 1 case.

Laboratory data in most instances were meager. The abnormal findings can be summarized as follows. In 1 case there was glycosuria, in 3, polycythemia. In 1 the dextrose tolerance curve was of the diabetic

TABLE 2—*Changes Following Removal of Tumor*

Cases	1	2	3	4	5	6	7
Return of periods	32 days	2½ mo	Uterus removed	4 days	Uterus removed	28 days	Uterus removed
Diminution of hirsutism	Normal 2 yr	Normal 9 mo	Normal 1 yr	No	Some, still shaved after 3 yr	Marked, still had to use depilatory	Marked
Return of scalp to normal	Yes	—	Yes	—	Yes	Yes	Yes
Return of voice to normal	Yes	—	Yes	—	Yes	Yes	Softer
Shrinking of clitoris	No mention	—	Yes	—	—	Yes	Same after 4 mo
Return of female habitus	2 yr	—	1 yr	—	Yes	Yes	Yes
Weight	—	—	—	Slight loss	35 lb lost (16 Kg)	—	Gain
Erythrocyte count	—	—	—	—	5,600,000	5,300,000	—

type. In 1 the sugar content of the blood was 150 mg per hundred cubic centimeters. For the patient who had glycosuria no values for blood sugar were reported. This patient was considered diabetic. In another case the chemical composition of the blood was reported as normal, but no values for sugar were given. Hormone studies, when done, showed absence of both the follicle-stimulating and the luteinizing gonadotropic substance. Estrogen was absent in Novak's case and consisted of 5,000 mouse units per liter in Saphir and Parker's and of 40 mouse units in twenty-four hours in Maxwell's.

As dramatic as the development of masculinity was the development of female traits following operative removal of the ovarian tumor (table 2). In the 4 instances in which hysterectomy was performed the first change to occur was the prompt return of a normal menstrual period, at the end of four days in 1 case, twenty-eight days in another, and thirty-two and seventy days, in the others. Once established, the

periods recurred regularly throughout the period of observation. Softening of the voice followed in every instance promptly, the change being noted as early as one and a half months. Where the male habitus had been established, the change in bodily configuration proceeded toward that of the female, so that in periods varying from one to three years the transformation was complete. With 2 exceptions hirsutism was likewise affected. The hair began to fall out, could be plucked more easily, became finer and grew more slowly. These changes were noted as early as three weeks after operation. In some instances the hair returned to the original status. In others at the end of the period of observation it was markedly diminished and softer, but still heavy enough to necessitate the use of depilatories or shaving at long intervals. In cases in which partial baldness had developed hair began to grow on the head again, until once more the distribution was feminine. One patient who was obese lost weight, another who had been lean gained. With 1 exception the clitoris diminished in size in all cases, even as early as three and a half weeks after operation. In 1 case (that of Novak and Wallis) the systolic blood pressure dropped from 145 mm before operation to 100 mm five months after operation. Also interesting was the diminution in number of red blood cells in cases of polycythemia. The most marked change was in Bingel's case, in which the count fell from 8,900,000, with 130 per cent hemoglobin, before operation to 5,500,000, with 100 per cent hemoglobin, one month after operation. The sugar content of the blood in Novak's case fell from 150 mg per hundred cubic centimeters (fasting specimen) before operation to 115 mg afterward. Hormone studies in the case of Saphir and Parker showed that the estrogen content, at first high, fell to low values. In Maxwell's case it reached zero. In the case reported by Novak and Wallis there were no gonadotropic or estrogenic substances.

*Pathologic Data* (table 3) —The tumor was in the right ovary in 4 cases and in the left in 3 cases. In 6 cases it was grossly evident, the largest tumor measuring 13.5 by 8 by 5 cm. The average tumor was equivalent in size to a chestnut. One growth was evident only microscopically (Saphir and Parker's case). Another (Maxwell's case), judging from its size in the histologic preparation, must have been about 1 cm in diameter. All the tumors were solid, felt cystic or rubbery and were oval and yellowish orange except one, which was reddish gray. Every one was completely or partially encapsulated, usually by thinned-out ovarian cortex. On section the tumor usually was lobulated by fibrous septums radiating in from the capsule. In 1 case the central portion contained an irregular patch of gray fibrous tissue. In some cases the growth occupied the medullary portion of the ovary. The tumor reported by Bovin was parovarian. In Sellheim's report the location was not clearly described.

*Microscopic Features of the Tumors*—In all specimens the tumor tissue was richly cellular, the cells forming no particular pattern. They filled in the spaces of a network formed by capillaries branching out from scattered large vessels. Fibrous stroma was scant following these vessels. In 2 cases stains for reticulum were used and revealed fine, silver fibrils encircling single cells or small groups of cells. In 1 instance the stroma was more richly fibrous and was described as a network formed by branching septums radiating in from the capsule. In the case reported by Saphir and Parker the growth consisted of a small nest of cells. The cells composing the tumor, in general, were uniform in type, relatively large and polyhedral, they had distinct outlines in 5 cases. The cytoplasm was granular, eosinophilic and variable in amount. Many of the cells appeared clear owing to the scant amount of cytoplasm dispersed by the fat content.

TABLE 3—*Pathologic Data in Cases of Ovarian Tumor*

Case	Condition of Uterus	Description of Tumor				Condition of Opposite Ovary
		Location	Size, Cm	Color	Solid	
1	Normal	Left	5	Yellow	Yes	—
2	Normal	Left	8.5×8×6	Orange	Yes	Small, sclerotic
3	Large fibroid	Left	Approx 4	Gray red	Yes	Small, sclerotic
4	Normal	Right	Microscopic	—	—	Normal
5	Large fibroid	Right	9×9×4	Orange	Yes	Small, sclerotic
6	Normal	Right	13.5×8×5	Orange	Yes	Small
7	Many fibroids	Right	Approx 1	—	Yes	Sclerotic

In 4 cases the clear cells predominated. In no instance in which chiomaffin granules or glycogen were looked for were they demonstrated. The nuclei were either oval or round, some were rich in chromatin, giving the body a dark appearance, others were vesicular. Nucleoli were observed in all. In addition to clear cells, others were present in which the cytoplasm was more abundant and fat was absent.

In the 3 remaining cases the tumor consisted, predominantly in 1 and exclusively in the other 2, of a densely eosinophilic cytoplasm. Fat was absent in 3. In 1 case (Maxwell) coarse brown granules were present in the cytoplasm. Degenerative phenomena were described in 5 cases. In 2 these consisted of frank necrosis. In the others there was disappearance of the tumor cells by atrophy and by fibrous replacement. In those cases in which ovarian tissue was present primordial and developing follicles were noted, but no corpus luteum other than dense hyalinized fibrous remains. In Maxwell's case even these were absent.

In all cases the tumor was benign—at least no recurrence took place during the period of observation. In 4 cases there was fibromyoma of the

uterus In 1 the uterus was smaller than normal In 3 there was fluid in the abdominal cavity, and in 2 there were adhesions of the tumor to adjacent structures The opposite ovary, free of tumor, was described either as of normal size or as small and atrophied

#### REPORT OF CASES

CASE 1—A woman of Spanish parentage, born in France, came under the observation of the outpatient service of St Vincent's Hospital in February 1935, when she was 23 years of age She had not menstruated since May 25, 1934, and believed herself pregnant In addition, she complained of severe headaches in the frontal region Her menstrual periods had begun at 14 years and were regular, occurring every twenty-eight days and lasting three days She married at 17 and had a baby at 18, whom she nursed for more than twelve months There were no other pregnancies, though contraception was not practiced For more than one year prior to the onset of amenorrhea she had noticed a marked overgrowth of hair on the face, chest, back and extremities

Examination showed her to be short and obese—61 inches (155 cm) tall and weighing 177 pounds (80.3 Kg) Three years before she had weighed 100 pounds (45.4 Kg) The obesity was chiefly of the trunk, neck and face, being less marked in the extremities No objective evidence of pregnancy was found The breasts were not large, no secretion was present There was no enlargement of the abdomen Vaginal examination disclosed a soft cervix and a small uterus in good position with no adnexal abnormality Marked hirsutism was noted The thyroid was palpable though not enlarged The blood pressure was 110 systolic and 70 diastolic

She attended the outpatient clinic for one month and then was not heard of again until May 25, 1937, when she was brought to the hospital because of severe renal colic, chills, fever and vomiting After a few days the acute symptoms subsided, and attention was focused on the remarkable hirsutism displayed Since her last visit to the outpatient clinic she had begun to shave, first the chest, in 1936, and later the face Whereas in the beginning she shaved the face once a week, soon it was necessary to do so daily The amenorrhea continued The voice had become deeper and headaches persisted, recurring at monthly intervals She had become nervous, timid and depressed about her condition There had been no change in libido

Physical examination on May 25 showed the blood pressure to be 90 systolic and 60 diastolic The patient was moderately obese, weighing 161 pounds (73 Kg), with female habitus The voice was slightly husky but still feminine There was pronounced hypertrichosis of the entire body, the hair being heavy, black, coarse and of definitely male distribution, with a decided beard and pudendal excess, extending above the umbilicus The arms and legs were heavily covered, as were the dorsal surfaces of the fingers and toes The eyes were prominent Her bodily contour was decided abnormal, with large flabby pendulous breasts, flabby fat cheeks, a double chin, and a definitely obese waistline and pelvic girdle There was marked hypertrophy of the clitoris, with some diminution in the dimensions of the vaginal tube, the cervix and the fundus uteri When the patient was conscious, it was impossible to demonstrate any adnexal abnormality During anesthesia, however, the right ovary was felt to be enlarged

Urologic study revealed a calculus in the left kidney, with infected hydro-nephrosis Roentgen examination of the skull, sella turcica and long bones revealed

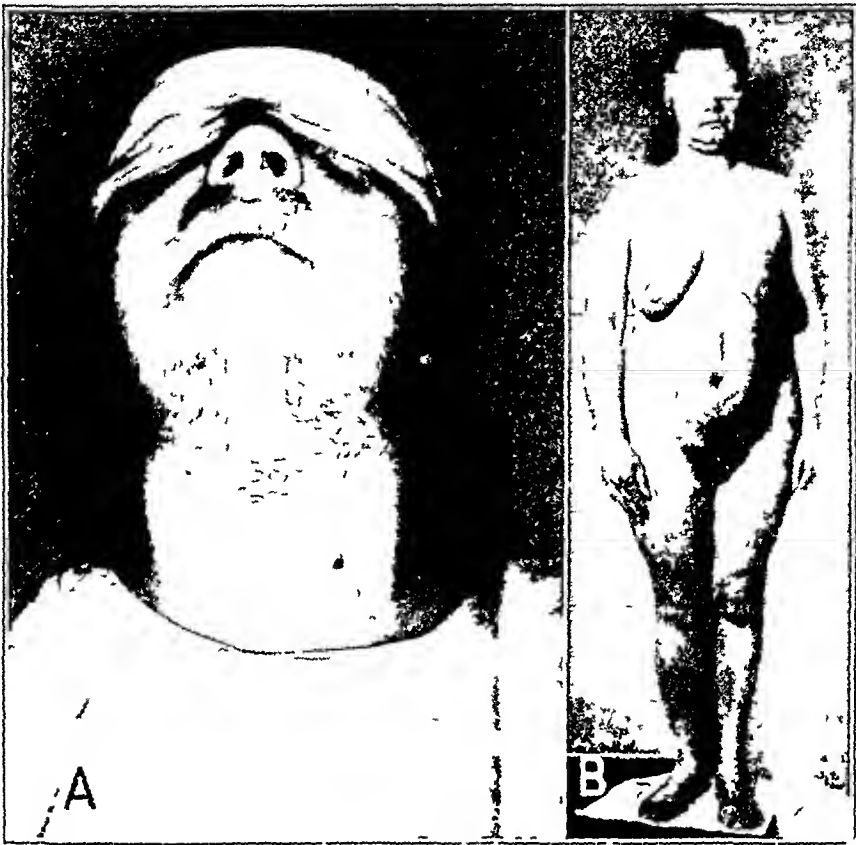


Fig 1 (case 1) —*A*, facial hirsutism before operation, two days' growth *B*, female habitus and generalized hirsutism on face, chest, abdomen and limbs. Breasts are flat and pendulous and the trunk, neck and face obese



Fig 2 (case 1) —Hypertrophy of the clitoris



no unusual changes other than what seemed like exostoses on the inner plate of the frontal bone. Aerograms of both adrenal regions failed to confirm the presence of any abnormality.

With subsidence of the renal disability, laparotomy was performed on June 16. Palpation and inspection of the pelvic viscera revealed that the uterus and tubes were normal, the left ovary seemed smaller than normal and so sclerotic that it could no longer function. Nothing suggestive of recent or old corpus luteum could be demonstrated in either ovary. The right ovary was enlarged, firmly resilient and of regular outline and had an unusually white tunica. It was removed after careful palpation of both renal and adrenal regions had failed to demonstrate any adrenal tumor. The patient made an uneventful recovery and was discharged on June 30.

*Laboratory Data*—The urine on entry contained albumin and numerous red and white blood cells. The blood count at this time showed 30,000 leukocytes, with 95 per cent polymorphonuclears and 5 per cent lymphocytes, 5,000,000 erythrocytes and 15 Gm of hemoglobin (Sahl). On discharge the white cell count had fallen to 8,480, with 66 per cent polymorphonuclear leukocytes and 34 per cent lymphocytes, the red cell count was 5,150,000. The urine became free from red cells, and the number of white cells diminished.

Chemical analysis of the blood showed 111 mg of sugar, 36 mg of nonprotein nitrogen, 432 mg of chlorides, 144 mg of cholesterol, 10.4 mg of calcium, 3 mg of phosphorus and 293 mg of sodium per hundred cubic centimeters. The carbon dioxide content was 47 cc per hundred cubic centimeters. The dextrose tolerance test showed 72 mg of sugar per hundred cubic centimeters during fasting, 124 mg half an hour after ingestion of 100 Gm of dextrose, 202 mg after one hour, 222 mg after one and one-half hours, 211 mg after two hours, 158 mg after three hours and 60 mg after four hours.

Tests for the follicle stimulating gonadotropic substance gave negative results. The estrogen content of the urine<sup>16</sup> was 3.3 rat units per liter. Two specimens assayed for androgenic substance<sup>17</sup> showed 17.3 and 15.7 international units.

*Postoperative Course*—On July 17 the patient had a normal menstrual period. By August 3 the voice had become higher pitched and the clitoris smaller, the hair on the body had begun to fall out and grow more slowly.

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16 Estrogen was extracted from a twenty-four hour specimen of urine by a method outlined by B. Harrow and C. P. Sherwin (*The Chemistry of the Hormones*, Baltimore, Williams & Wilkins Company, 1934, p. 167). The extract was taken up in oil and given to Dr. H. C. Taylor, of the New York University Medical College, Department of Gynecology, who assayed it by injecting it into rats.

17 Two twenty-four hour samples of urine were extracted after the method of Funk and Harrow (Harrow, B., and Sherwin, C. P. *The Chemistry of the Hormones*, Baltimore, Williams & Wilkins Company, 1934, p. 157). These were taken up in 25 cc of oil and assayed by Dr. W. K. Cuyler, of the Cleveland Clinic Foundation Hospital. Each sample was injected into a group of birds, 1 cc per day being given to each bird. The experiment was controlled by means of a group of birds which received 1 international unit of androsterone per bird per day, after the manner of T. F. Gallagher and F. C. Koeh (*Quantitative Assay for Testicular Hormone by Comb-Growth Reaction*, *J. Pharmacol. & Exper. Therap.* 55:97, 1935). Dr. Cuyler criticized the method we adopted for extracting the urine, on the ground that the yield by this method is only about 60 per cent.

On October 12 she was readmitted to the hospital, and a calculus was removed from the pelvis of the right kidney. Her convalescence was uneventful, and she was discharged on November 5. The blood pressure was 78 systolic and 14 diastolic. The dextrose tolerance test at this time showed 74 mg of sugar per hundred cubic centimeters during fasting, 191 mg one hour after ingestion of dextrose, 140 mg after two hours, and 25 mg after three hours (she felt dizzy at this point). The basal metabolic rate was +25 per cent and on repetition of the test +10 per cent.

She was seen again on November 3. She appeared happy, was slimmer and weighed 141 pounds (64 Kg). The hairs on her body were softer, less dense and lighter. She now shaved every two weeks. The periods were recurring regularly. The headaches had disappeared entirely.

On December 4 she reported that she had menstruated normally in November. She had allowed the facial hair to grow for three weeks so that a photograph could be taken. A definite beard was present, but it was much lighter and scantier than what grew in two days before operation.



Fig 3 (case 1)—Facial hirsutism six months after operation, three weeks growth

On Feb 14, 1938, menstruation was reported as normal. A dextrose tolerance test by the Rose-Exton method showed 80 mg per hundred cubic centimeters during fasting, 143 mg half an hour after ingestion of dextrose and 160 mg after one hour. She was shaving once every two weeks.

In April menstruation was still normal. The patient weighed 140 pounds (63.5 Kg). The hair on the chest had disappeared. There was still a slightly greater amount than normal on the limbs. She continued to shave on an average of every two weeks. The double chin was almost gone.

*Pathologic Report*<sup>18</sup>—The specimen was an oval, resilient mass weighing 22 Gm unfixed and measuring 4.5 by 1.5 by 1.5 cm. The outer surface was smooth, even, shiny and pearly gray.

18 The technic of study was as follows. One half of the specimen was saved for display in the museum, the other was cut into many blocks. These were fixed separately in a 10 per cent dilution of solution of formaldehyde U. S. P., and

Section exposed a solid, sharply demarcated, spherical nodule, 3 by 2.5 cm, composed almost entirely of orange-colored tissue, except for the central portion, where there were small, irregular, gray areas. Fine strands of the same gray tissue divided the orange mass into small lobules. The nodule lay eccentrically in a tough, fiberlike capsule, which at one pole was only 1 mm thick and tough. At the opposite pole, the region of the hilus of the ovary, the capsule was thicker (5 cm) and more spongy, owing to the presence of many small, thick-walled vessels.

*Microscopic Examination*—The nodule was composed of a uniform type of cell laid down in continuous sheets between the numerous branches of the vascular

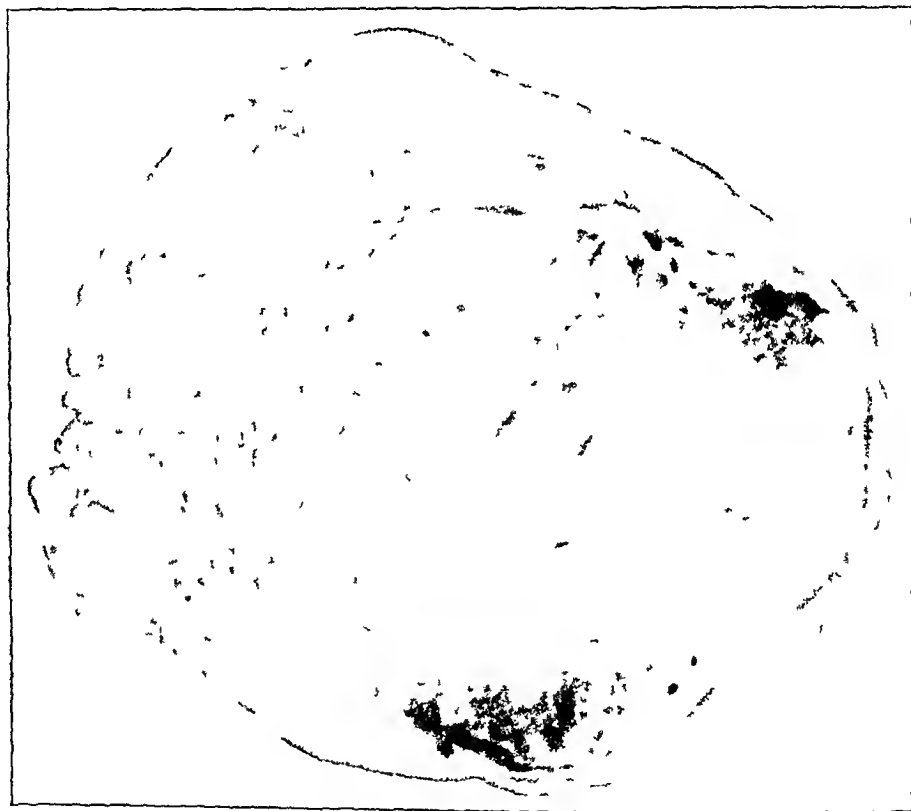


Fig. 4 (case 1) —Solid orange-colored nodule encapsulated by thinned-out ovary

in Zenker, Bouin, Regaud, Mann and Bensely solutions. They were embedded in paraffin and the sections stained with the following solutions: hematoxylin and eosin, the Weigert stain for elastic tissue, the Masson trichrome stain and the Foot and Foot stain for reticulum. Vines' stain (Broster, L. R., and Vines, A. W. C. *The Adrenal Cortex. A Surgical and Pathological Study*, London, H. K. Lewis & Co., Ltd, 1933) was used to demonstrate the possible presence of fuchsinophilic granules. The fat content was studied with scarlet red and osmic acid. Blocks fixed in absolute alcohol were embedded in pyroxylin and stained with Best's carmine stain in order to demonstrate the presence of glycogen. Granules of chromaffin were looked for in material fixed in Regaud's solution.

tree The larger vessels, of which there were many, were surrounded by moderate amounts of connective tissue, which diminished as the twigs became smaller Distributed about the capillaries and surrounding cells individually and in small groups was fine reticulum demonstrated with silver No elastic tissue was seen other than that forming part of the walls of the blood vessels

The tumor cells varied slightly in size, from about 10 to 16 microns The membranes stood out distinctly, outlining their oval, round, irregular and polyhedral shapes The cytoplasm was granular, eosinophilic and for the most part scant, so that in the hematoxylin and eosin preparation the cells looked clear This was due to fat being dissolved out of the paraffin-embedded sections Other substances, such as glycogen, chromaffin and fuchsinophilic granules, were absent In material fixed in Bouin's solution, the stained granules were especially

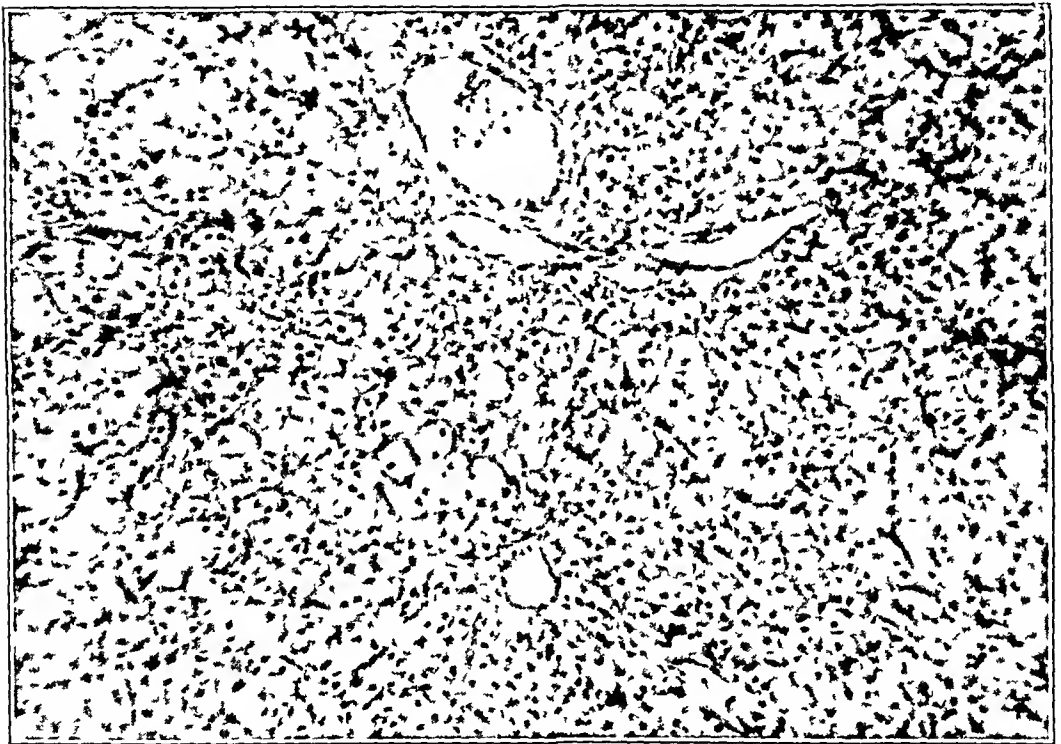


Fig 5—Photomicrograph, low power, hematoxylin and eosin stain, showing large polyhedral cells, clear cytoplasm and distinct cellular outlines

fine and so arranged as to give the cell a foamy appearance In material fixed in other solutions the granules were coarser and clumped about the nucleus The nucleus was seen to best advantage in tissue fixed in Mann's solution It was of moderate size and oval or round—variously located in the cell—and had a thick, sharp nuclear membrane, a nucleolus and a small amount of chromatin Less common were irregular masses of similar but smaller cells in which fat was scant or absent The cytoplasm of these cells appeared more eosinophilic, since it was less spread apart by lipid content Also present were groups of small, shrunken cells entangled in thickened hyalinized reticulum In some places there were areas composed almost entirely of the latter material This change, evidently a degenerative one, was most marked in the central gray portion of the nodule

The capsule was seen to consist of thinned cortex of ovary In it there were primordial follicles, small developing follicles and compact hyalinized fibrotic rem-

nants of old corpora lutea. Whatever tissue of the underlying medulla remained unoccupied by tumor was thinned out about its periphery.

Curettage produced a small bit of tissue, which disclosed a thin layer of endometrium containing occasional small glands lined with tall epithelial cells. The nucleus lay at the base of each cell. The stroma cells were small, with scarcely any cytoplasm.

CASE 2<sup>19</sup>—The patient was first observed in 1923, at the age of 25. She had been married one year and had not become pregnant. Physical examination disclosed an enlarged uterus. At operation the tubes and ovaries were normal, but the uterus, which was smooth and symmetrically enlarged by a fibroid, was removed.

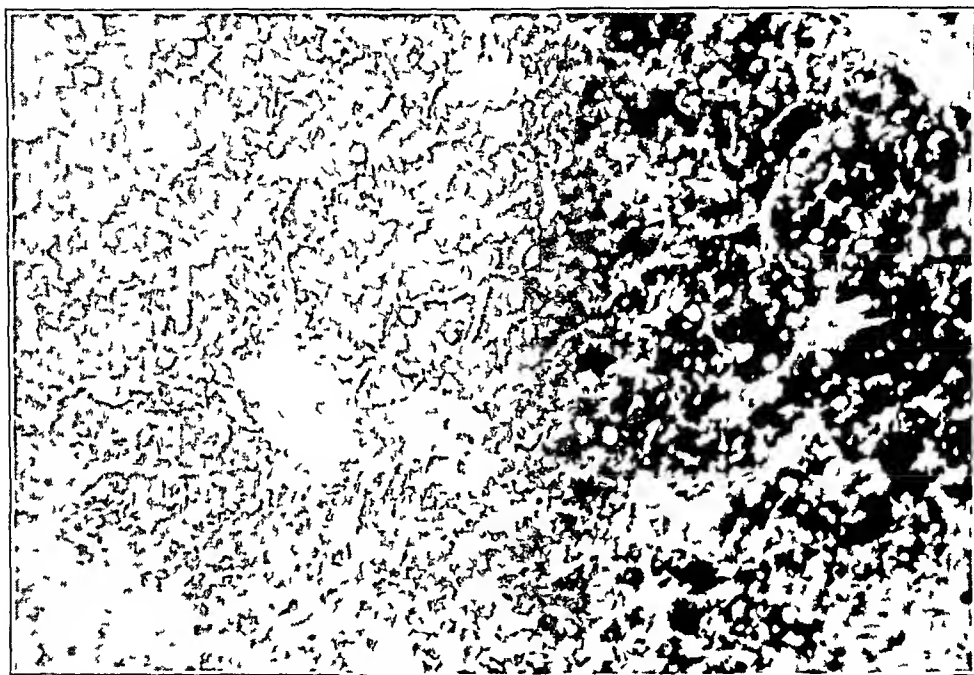


Fig. 6—Section stained with osmic acid, showing heavy reaction.

During a routine examination five years later an abdominal tumor and fluid were discovered. She had no complaints other than that her voice had become deeper soon after the operation and, further, that the amount of hair over her body had progressively increased, so that she found it necessary to shave. On examination the blood pressure was 130 systolic and 70 diastolic and the pulse rate 112. The heart and lungs were normal. The abdomen was soft. Fluid was evident, as was a hard, nontender mass in the right lower quadrant. There was an abnormal growth of hair of male distribution over the abdomen, legs, arms and face. The habitus was female.

Vaginal examination revealed a normal clitoris and a small, healthy introitus with a freely movable cervical stump. The cul-de-sac was filled with a hard, fixed, irregular tumor, continuous with the abdominal mass. The left broad ligament was thickened. On this side a small growth was likewise palpated.

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<sup>19</sup> This case is included with the permission of Dr. William S. Smith, of the Brooklyn Hospital.

*Laboratory Data*—A blood count showed 4,500,000 erythrocytes, 83 per cent hemoglobin and 11,200 leukocytes, with 80 per cent polymorphonuclears, 2 per cent eosinophils, 2 per cent monocytes and 16 per cent lymphocytes

*Operation*—On April 23, 1928, 2 quarts (1,893 cc) of fluid was present in the peritoneal cavity. Both ovaries were occupied by solid growths. That on the right was lobulated. The one on the left was the size of a goose egg. Both were adherent to bowel and bladder. After the adhesions had been freed it was possible to remove the ovaries. Recovery was uneventful. Dr James Denton, pathologist, reported the specimen as consisting of several irregularly shaped masses, each 3 or 4 cm in diameter, having a deep yellow-orange color. The histologic diagnosis was bilateral ovarian luteoma.



Fig 7 (case 2)—Section stained with hematoxylin and eosin (low power), showing polyhedral shape, large size, distinct cellular outlines and clear cytoplasm

*Postoperative Course*—On discharge, on May 14, her general condition was excellent. The cervical stump was fixed and the vaginal vault indurated. On May 24 high voltage roentgen therapy was begun.

On July 24 the voice was not nearly so deep. The excess hair on the body was disappearing. Vaginal examination showed the cervix to be free and movable and the vaginal wall soft and pliable. The patient appeared and felt well.

She remained free from symptoms until October 1931, when her voice again began to deepen and the body hair started to grow to excess. Vaginal examination revealed a hard mass, the size of a marble, behind the cervix. In the belief that there was a recurrence, roentgen therapy was resumed.

On December 9 a hard walnut-sized nodule was discovered in the abdominal scar, and the pelvic tumor was noted to have increased in size.

On Jan 8, 1932, she was operated on again. The intestine was infiltrated with tumor adherent to that present in the abdominal wall. In the pelvis, behind the

sacral promontory, was a mass, 7.5 by 5 cm. The growth was found to be inoperable. She recovered from operation, but in three months intestinal obstruction developed, and she reentered the Brooklyn Hospital in March. Intestinal anastomosis was performed. She grew worse and died on July 7.

It had been noted that her voice was deeper and that the amount of hair on the body had increased. No autopsy was done.

*Microscopic Examination*—A biopsy specimen from the abdominal nodule showed identical structure with that of the original ovarian growth. The evidence definitely indicated tumor of the corpus luteum, though the question of carcinoma of an adrenal rest was raised. It was our privilege to examine a microscopic preparation of the original growth in the ovary, a description of which follows.

The tumor microscopically was composed of a uniform type of cell with a thick, distinct border. The cells were about 8 to 16 microns in breadth and polyhedral. The cytoplasm was granular and eosinophilic and in some cells abundant and in others scant, giving the cell in the latter instance a clear appearance. Though no stains for fat were employed, the appearance of the cytoplasm strongly suggested the presence of fat. No granules of pigment were evident. The nuclei were of moderate size. Chromatin was abundant and coarsely granular. Nucleoli were present. The tumor was traversed by many small blood vessels, from which radiated capillaries, forming a network in which the tumor cells lay in cords and sheets. Because the capillaries were collapsed, the first impression was that the tumor was composed of a solid sheet of cells. In one portion, equivalent to about one third of the section, there was complete necrosis of the tumor.

#### COMMENT

Our first case certainly was an instance of the condition under discussion, for clinical masculinity developed in a patient who previously had been completely feminine. Further, an orange-colored nodule composed of large clear fat-containing cells occupied the medulla of the right ovary. Lastly, the reversal of symptoms following removal of the right ovary established it as the sole and primary site of the growth. In the second case (Smith), though histologically an instance of the same condition, there were certain atypical features. The hysterectomy prevented the establishment of nonsurgical amenorrhea, the tumor was bilateral and malignant. Since in the other reported cases and in ours the growths were benign, the possibility of metastasis in Smith's case is suggested. In refutation, we have the established clinical fact that the symptoms receded after removal of the growth, only to reappear with recurrence of the growth.

Concerning the nature of the tumor, we are as much in the dark as were our predecessors. Various physicians who have studied slides made in our case (E. Novak, R. Meyer, W. Schiller and D. Symmers) have expressed the belief that the growth arose from an adrenal rest. Vines, who with Broster<sup>20</sup> made a special study of adrenal tissue in cases of the adrenogenital syndrome and who examined slides made in our

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<sup>20</sup> Broster, L. R., and Vines, H. W. C. *The Adrenal Cortex. A Surgical and Pathological Study*, London, H. K. Lewis & Co., Ltd., 1933.

case, stated emphatically that the growth was not of adrenal origin and suggested luteinic origin instead. Otto Saphir, who also studied a slide, came to the conclusion that the appearance was not similar to that in his case, which he felt was an instance of true adrenal rest, while ours was one of true tumor-luteoma or hypernephroid.

The facts in favor of the theory that the tumor arose from an adrenal rest were

- 1 It was orange colored
- 2 Its component cells resembled those of adrenal cortex
- 3 Adrenal cortical tumors have produced similar syndromes (Bullock and Sequeira <sup>21</sup>)

4 Adrenal cortical tumors producing masculinization have been reported outside the adrenal gland (Kolodny <sup>22</sup>)

5 Adrenal rests have been described along the course followed by the ovary in its descent and within the ovary itself (Meyer <sup>23</sup>). The authenticity of a true adrenal rest in the ovary proper was contested by Glynn <sup>2</sup>

6 The presence of a distinct cellular membrane has been offered as evidence favoring its adrenal origin by Schiller <sup>24</sup>. This argument, in our opinion can hardly be valid, since it is not unusual to see distinct outlines in cells which are fatty and clear. Examples are the cells of renal hypernephroma, lutein cells during regression of the corpus luteum, hepatic cells during so-called cytolytic degeneration and the cells of so-called corpus luteum tumor associated with femininity, which will be described later.

7 It is doubtful whether a cell as highly differentiated as a lutein cell can give rise to a tumor.

8 Further doubt is cast on the origin from corpus luteum when one considers that the function of the corpus luteum is to regulate the endometrium preparatory to nidation, a function far removed from the production of masculinization.

In favor of the tumor's luteinic origin authors have pointed to the following facts, some of them the same as in the preceding group.

- 1 The tumor is of yellow-orange color
- 2 Its cells resemble those of corpus luteum. The cells of the latter, however, appear similar only when the corpus luteum regresses.

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<sup>21</sup> Bullock, W., and Sequeira, J. A. On the Relation of the Suprarenal Capsule to the Sexual Organs, *Tr. Path. Soc. London* **56**:189, 1905.

<sup>22</sup> Kolodny, A. Suprarenal Virilism in a Woman. Tumor of an Extrarenal Suprarenal Rest, *J. A. M. A.* **102**:925 (March 24) 1934.

<sup>23</sup> Meyer, R. Personal communication to the authors.

<sup>24</sup> Schiller, W., in discussion on Rottino, A. Ovarian Adenoma Associated with Masculinization, *Arch. Path.* **25**:928 (June) 1938.



3 The tumor in question inhibits full development of graafian follicles and ovulation, as does corpus luteum, thus leading to amenorrhea

4 Bergstrand<sup>15</sup> cited the work of Steinach and Kun, who injected extract of corpus luteum into young spayed female guinea pigs and noted virilizing effects

Meyer<sup>25</sup> countered by asking what virilizing symptoms in a female guinea pig were

Inconclusive as the aforementioned arguments may be, they nevertheless indicate that an adrenal rest is a more probable source of origin than corpus luteum

The subject of hypernephroid and luteoma is complicated further by another group of tumors also labeled luteoma. These are associated not with masculinization but rather with a clinical picture analogous to that produced by granulosa cell growths. The subject was reviewed in 1917 by Glynn,<sup>2</sup> who said that 14 tumors described as ovarian hypernephromas were analogous to 9 others described in the literature as lutein growths. Novak and TeLinde<sup>26</sup> questioned the nature of 5 of them and gave evidence that they were of other origin. Other contributions followed under different headings, such as *folliculome lipidique* (La Cene<sup>27</sup>), granulosa cell tumor (Plate,<sup>28</sup> Benda and Krause<sup>29</sup>) and luteoma or corpus luteum tumor (Wolf,<sup>30</sup> Wills and Romano,<sup>31</sup> Cutler<sup>32</sup>)

The clinical features described in the later reports were similar to those in the cases reviewed by Glynn, except that some of his patients were older—in the fifth, sixth and seventh decades—whereas in the later cases the patients were 21, 22, 23, 26 and 38 years of age. In no case were there symptoms of masculinization. The chief disorder was excessive and prolonged bleeding for two to six months, followed in 3 cases by amenorrhea. In 1 case the breasts enlarged, and in 2 a secretion could be expressed. In the 1 instance in which the endometrium was

25 Meyer, R. Ueber die Natur der virilisierenden Ovarialtumoren, *Ber u d ges Gynak u Geburtsh* **27** 113, 1934

26 Novak, E., and TeLinde, R. The Pathological Anatomy of the Corpus Luteum, *Bull Johns Hopkins Hosp* **34** 298, 1923

27 La Cene, cited by Plate<sup>28</sup>

28 Plate, W. P. Eine seltene Form eines Granulosazelltumors des Ovariums, das sogenannten "Folliculomelipidique," *Arch f Gynak* **153** 318, 1933

29 Benda, R., and Krause, E. J. Luteinisierte Granulosazeltumor mit Amenorrhoe, *Arch f Gynak* **157** 400, 1934

30 Wolf, S. A. Luteoma, *Am J Obst & Gynec* **13** 575, 1927

31 Wills, S. H., and Romano, S. A. A Case of Luteoma, *Am J Obst & Gynec* **29** 845, 1935

32 Cutler, O. I. Corpus Luteum Tumor, *Am J Obst & Gynec* **30** 131, 1935

studied it was hyperplastic. Removal of the tumor-bearing ovary resulted in reappearance of menstruation in the patients with amenorrhea and the establishment of normal bleeding in those with menorrhagia.

All but 1 of the tumors were unilateral. None was reported malignant. They were solid. In 1 tumor there were areas of degeneration causing formation of small cysts. Their size varied. 1 measured 15 by 10 by 5 cm. and another 3.5 by 4.5 by 6 cm. The growth occupied the central portion of the ovary, the cortex of which was stretched into a thin capsule around it. The one exception was that in the case of Benda and Krause. There was an almond-shaped, flattened ovary on the medial aspect of the tumor, from which it could be separated. The tumor was usually yellow, with scattered irregular areas of fibrous tissue. Grossly, therefore, the tumors resembled those of the so-called hypernephroid group.

Histologically they were very cellular. In two reports (Wills and Romano, Wolf) the cells were said to be arranged in alveoli of varying sizes surrounded by fibrous septums. The tumor cells were large, irregular and polyhedral, with distinct outlines and a granular eosinophilic cytoplasm which for the most part was scant. The nuclei were flattened out against the cellular membrane by contents strongly suggesting fat.

In Cutler's case, a slide from the tumor in which we had the opportunity to study, the arrangement of the cells was different. Here they formed large masses, filling in a meshwork made of capillaries. Fibrous tissue was scant. A moderate number of cells were clear, owing to their fat content. Most cells, however, contained an abundance of eosinophilic, granular cytoplasm. The nuclei were large, of uniform size and oval or round, with a distinct nuclear membrane, evenly distributed granular chromatin and a distinct nucleolus. None of the nuclei were displaced. Microscopically therefore, a difference existed between the tumor in Cutler's and those in the other 2 cases. The same is true of the histologic appearance in the cases reported by Benda and Krause and by Plate. In the former authors' case the tumor cells were arranged in various patterns: diffuse masses, rosette-like structures and long columns. Many cells appeared frothy and clear, owing to their fat content. In Plate's case the tumor cell was essentially cylindric and filled with fat. The cells were arranged in various patterns: rosettes, columns and alveoli. In both cases the growths were evidently of the granulosa cell type, the tumor cells being filled with lipoid.

After we had reviewed all these cases it appeared evident that the histologic pattern of the growths was variable, making it difficult to identify the tumors as similar on a histologic basis alone. This difficulty pertained particularly to the first 3 cases (Wolf, Wills and Romano, Cutler), the others being more easily identified as instances of granulosa cell tumor. If the first 3 tumors were similar to the others then they

also were granulosa cell tumors, differing only in the degree of fatty change, and should be classified as such and not as corpus luteum tumors. Whether the fatty change was due to the luteinizing factor responsible in changing normal granulosa cells into those constituting corpus luteum is of course something one can only philosophize about. Nevertheless, if that should be the case, one would have a reasonable basis for expecting the variable histologic picture of the group, for then it could be ascribed to different degrees of differentiation of a tumor whose histologic picture to begin with is variable.

The confusion of names that exists is understandable. The 5 feminizing tumors, like the masculinizing growths, bore a superficial resemblance to corpus luteum, from which many have been named. However, the biologic effects of the two types of tumor were so different and were so unlike those associated with the corpus luteum that it is dangerous to regard them as both arising from this body. It would simplify matters if it were possible to adopt some acceptable and appropriate name for the masculinizing tumor. If its origin from adrenal gland were certain, it should be called an adrenal hypernephroma rather than a hypernephroid. Since this matter is in dispute, we suggest a name descriptive of its biologic properties—masculinovoblastoma. This differentiates the growth from the other masculinizing tumor, the arrhenoblastoma, and the feminizing one, more appropriately referred to as a luteinized granulosa cell growth.

Though the masculinovoblastoma may be primarily responsible for stimulating growth of hair, hypertrophy of the clitoris and inhibition of factors which play a role in the menstrual cycle, there is reason to feel that there is an interplay with the pituitary gland. This is suggested by the fact that although menstruation returns promptly after operation, the effect on hirsutism is not so complete. To be sure, changes in texture and in rate of growth begin in some cases promptly, nevertheless, the hairs still grow even after one and a half years. In other words, the stimulating factor still persists. Other evidence suggesting outside influences is also present. Several of the patients had disturbances in carbohydrate metabolism, as shown by glycosuria, hyperglycemia and a diabetic type of dextrose tolerance curve, which might be explained on the basis of diminished pituitary action. Most interesting is the fact that a dextrose tolerance curve obtained in our case six months after the tumor was removed was still abnormal, indicating a continuing action of a factor outside the ovary, most likely pituitary. Polycythemia, present in several cases, suggests the same possibility. Moehlig and Bates<sup>33</sup> reported 2 cases of polycythemia in persons with pituitary basophilism. Further evidence to support an ovarian tumor-pituitary interplay was added by

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33 Moehlig, R. C., and Bates, G. S. Influence of the Pituitary Gland on Erythrocyte Formation, *Arch Int Med* 51: 207 (Feb.) 1933.

Norris,<sup>34</sup> who reported on the autopsy in a case of arrhenoblastoma. He described degranulation and hyalinization of the cytoplasm of the basophils in the pituitary gland. According to Crooke,<sup>35</sup> this change is seen more regularly in pituitary basophilism than in adenoma formation.

This interplay of a gland with the pituitary body is not at all unique for the ovary. It was suggested by Graef and associates<sup>36</sup> in a report of hirsutism, obesity and hypertension in a girl with adrenal carcinoma. The pituitary gland in that case likewise showed peculiar changes in the granules of the basophils.

#### SUMMARY

A new group of ovarian tumors associated with masculinization, different from the arrhenoblastoma, has been recognized for some time.

Seven cases reported in the literature are accepted as examples of this tumor. The 2 reported here bring the total to 9.

In only 1 case was the growth proved malignant.

Removal of the tumor results in recession of symptoms.

The histogenesis of the tumor is in doubt. There is much to favor its origin from an adrenal rest. Some authors, however, lean to a luteinic origin.

The tumor was unilateral (in 8 of 9 cases), solid yellow or orange, composed of large cells and in some cases clear owing to fat content, while in others, in which no fat was present, the cytoplasm was not clear.

The pathologic differentiation between the masculinizing tumor and the feminizing luteoma may be difficult.

It is suggested that the term masculinoblastoma be adopted for the masculinizing tumor, to distinguish it from the arrhenoblastoma and the feminizing luteoma.

Clinical evidence suggests an interplay of the growth with the pituitary gland.

NOTE—Since May 1938, when this article was submitted for publication, the following events have occurred to our patient.

On June 7 she presented herself in the outpatient department because she had failed to menstruate in May. Finding an enlarged, soft uterus, the examiner made a diagnosis of pregnancy. A Friedman pregnancy test performed three days later gave a positive result. A dextrose tolerance test on this day showed 68 mg

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34 Norris, E. H. Arrhenoblastoma, *Am J Cancer* **32** 1, 1938.

35 Crooke, A. C. Changes in the Basophilic Cells of the Pituitary Gland Common to Conditions Which Exhibit the Syndrome Attributed to Basophilic Adenoma, *J Path & Bact* **41** 339, 1935.

36 Graef, I., Bunim, J. J., and Rottino, A. Hirsutism, Hypertension and Obesity Associated with Carcinoma of the Adrenal Cortex. Indeterminate Pituitary Adenoma and Selective Changes in Beta Cells (Basophils) of Hypophysis, *Arch Int Med* **57** 1085 (June) 1936.

of sugar per hundred cubic centimeters of blood during fasting, 108 mg one half hour after the ingestion of 100 Gm of dextrose, 137 mg after one hour, 58 mg after two hours and 88 mg after three hours

She was not seen again until August 19, when severe ureteral colic forced her to return to the hospital. It was elicited that she had had a normal menstrual period on June 19, on July 17 and a few days before the current admission. All periods had been normal. She was firm in her denial that an abortion had been induced. It was further elicited that she was gaining weight and had to shave with increasing frequency. Pelvic examination now revealed a normal-sized uterus. A small, tender mass was felt in the left adnexal region. The status of hirsutism was the same as at the first admission, with the exception that the hairs were finer and lighter. Friedman tests on this admission gave repeatedly negative results.

On September 14 the left tube and ovary were removed. The latter was found adherent in the cul-de-sac. She recovered from her operation and was discharged on October 16. In the interval that followed she suffered from hot flashes and headaches, which were controlled more or less by administration of estrogenic substances. Of particular interest was the definite change in the rate and character of growth of hair. For the first time since any operative intervention had been made she was able to postpone shaving for six weeks, until November 22. When next seen, on December 2, she had not shaved. She appeared slimmer, the texture of the skin was soft and smooth, and the facial hairs, though increased, were much lighter and finer than theretofore. On March 21, 1939, she presented herself on request. She weighed 150 pounds (68 Kg) and appeared moderately obese. The rate of growth of facial hair had increased so that she shaved every other day.

We wish to note further that two other papers<sup>37</sup> dealing with the ovarian tumor in question in addition to those already referred to have appeared.

*Pathologic Report*—The specimen consisted of a tube and ovary with its mesentery. The tube appeared normal except for a few peritoneal adhesion tags. The ovary was of normal size, measuring 32 by 35 by 15 mm and weighing 123 Gm. The surface was smooth and nodular, owing to the presence of eight thin-walled cysts filled with clear straw-colored fluid. One contained blood. They measured from 4 by 3 to 7 by 3 mm. Two bodies were found adjacent to each other, measuring 6 by 3 and 6 by 2 mm, respectively. Each had a thin, wavy, golden-yellow margin 1 mm thick. The center of one was cystic and that of the other solid, being occupied by a gray fibrous tissue. In addition, there was a third body 7 by 3 mm close to the surface, with an orange-colored margin and a gray fibrous core. Macroscopically all three were interpreted as regressing corpora lutea.

The entire ovary was cut into serial blocks, and histologic sections were made from each. Microscopic examination of these showed many primordial follicles with normal-appearing ova. The cysts noted grossly were seen to be of the theca lutein variety. The yellow bodies were composed of large irregular clear cells similar to those composing the tumor removed with the first ovary. There were no features, however, distinguishing them from cells of regressing corpus luteum. It was concluded, therefore, on anatomic grounds that in this ovary the yellow bodies were corpora lutea.

Dr Franz Yost collaborated in this study

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<sup>37</sup> Novak, E. Masculinizing Tumors of the Ovary (Arrhenoblastoma, Adrenal Ovarian Tumors), *Am J Obst & Gynec* **36** 840, 1938. Reis, R. A., and Saphir, O. S. Masculinizing Elements in the Ovary, *ibid* **35** 954, 1938.

# THE PRECORDIAL LEAD

## I FINDINGS FOR PATIENTS WITH NORMAL HEARTS AND THOSE WITH HEART DISEASE OTHER THAN MYOCARDIAL INFARCTION

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Since the introduction of the use of the precordial lead in clinical electrocardiography, as the result of the work of Wilson<sup>1</sup> and of Wolferth and Wood,<sup>2</sup> enough data have been accumulated to establish it as a helpful and at times necessary procedure in the diagnosis of cardiac disorders. But as frequently occurs with any new procedure, further study becomes essential to define its limitations and its proper value. After the three conventional leads were first introduced into general use, physicians had to become familiar with the wide range of variations in normal electrocardiograms before they could interpret any abnormality. Moreover, it was quickly found that many factors besides disease of the heart could alter the form of the tracings. Among these factors were the effect of digitalis and of the drinking of ice water on the T wave and the alterations that resulted from deep breathing, from the presence of fluid in either pleural cavity or from a change in the position of the body. In fact, significant abnormalities were found to result from other causes, such as disturbances in the calcium or bodily

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From the Medical Clinic of the Peter Bent Brigham Hospital

Read in part at the meeting of the New England Heart Association, Boston, Jan 24, 1938

1 Wilson, F N, in discussion on papers of Koltz and Lloyd, Warthin, Conner and Holt, Scott, Feil, Katz and Moore, and Carter, Tr A Am Physicians 45 168, 1930. Wilson, F N, Barker, P S, Macleod, A G, and Klosternmyer, L L. The Electrocardiogram in Coronary Thrombosis, Proc Soc Exper Biol & Med 29 1006, 1932. Wilson, F N, Macleod, A G, and Barker, P S. The Distribution of the Currents of Action and of Injury Displayed by Heart Muscle and Other Excitable Tissues, University of Michigan Studies, Scientific Series, Ann Arbor, Mich, University of Michigan Press, 1933, vol 10, p 22

2 Wolferth, C C, and Wood, F C. The Electrocardiogram in Coronary Thrombosis, Am J M Sc 183 30, 1932

metabolism accompanying diseases of the endocrine glands, e g , myxedema, hyperthyroidism, hypoparathyroidism and hyperparathyroidism. It is evident, therefore, that similar studies are now necessary to ascertain the changes that occur in the precordial lead under a great variety of circumstances. Only in this way can reliable and decisive criteria be established that will aid in the diagnosis of myocardial infarction. For it is with respect to this condition that the precordial lead is proving to have its main value.

Technical difficulties have already arisen and likely will continue to do so to some extent, for they are inherent in this new method. Whereas with the three conventional leads it mattered little or not at all which part of the forearm or left leg was employed or even what the size of the electrode was, it quickly became clear that slight variations in the exact location over the precordium to be explored produced profound changes in the form of the electrocardiogram. From a practical point of view, it becomes highly desirable, if possible, to have not only a uniform procedure but one that is simple and that elicits all the significant data.

#### METHOD OF STUDY

As the main purpose of this study was to find one optimum point over the precordium from which lead IV should be taken, a series of 9 or 10 tracings were obtained from different parts of the chest. The points selected are indicated in figure 1. It was hoped thereby if possible to find a single position which would show significant alterations when myocardial infarction was present and would fail to show such changes when myocardial infarction was absent. It is obvious that the point of preference would be that place at which under normal circumstances the deflections of the electrocardiographic waves are greatest, for it is the inversion or the absence of these same waves that lays the foundation for the detection of the presence or absence of myocardial infarction. By this means the significance of minor alterations becomes less confusing.

The three features that were particularly studied were the absence or amplitude of the Q wave, the direction and amplitude of the T wave and the deviation of the ST segment from the isoelectric line. These three aspects of the electrocardiograms were investigated because they are the ones that have been studied and found to be useful in the making of a diagnosis. It is our purpose to focus attention on the preference and reliability of the data obtained from around the apex of the heart, i e , the eighth and ninth positions.

For all the tracings the old polarity was used, with the right arm electrode as the exploring electrode at the precordium and the left leg

electrode as the indifferent electrode<sup>3</sup> The electrode used was of the standard German silver type, measuring  $1\frac{1}{2}$  by 2 inches (3.8 by 5 cm), and its long diameter was placed parallel to the long axis of the body. We secured 526 tracings for 352 patients. Sixty-four of these patients subsequently came to autopsy, and we had the opportunity of correlating the electrocardiographic findings with the postmortem data.

For purposes of this study it is required that a normal precordial tracing should have a Q wave of 2 mm or more and an inverted T wave. A tracing was regarded as indicative of myocardial infarction if the Q wave was absent. It was regarded as questionably indicative if the

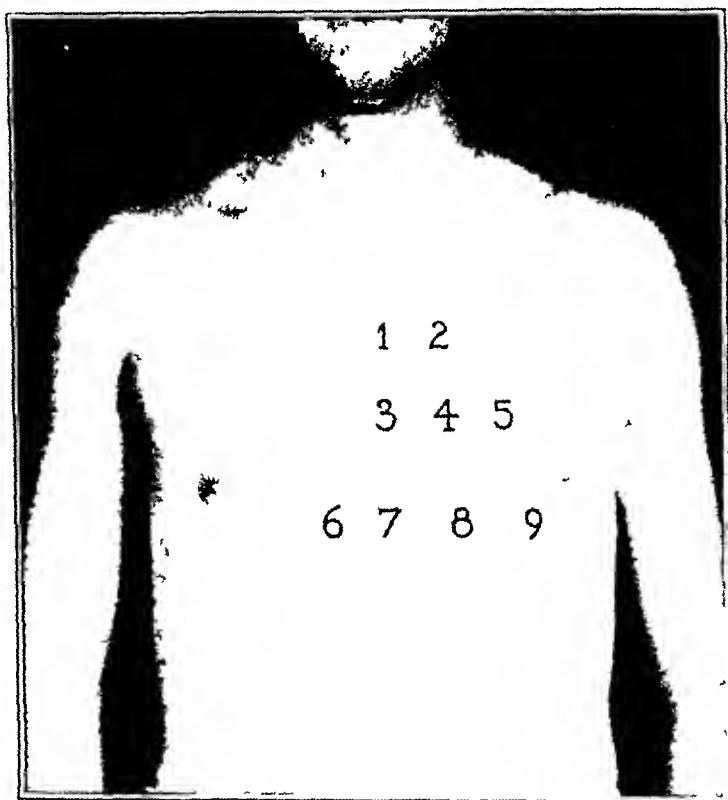


Fig 1—The numbers indicate the nine positions from which the precordial leads were taken throughout this study. 1 indicates the position in the midline in the second interspace, 2, 4 cm to the left of the midline in the second interspace, 3, 4 and 5, in the midline, 4 cm and 8 cm, respectively, to the left between the third and fourth interspaces, 6, 4 cm to the right in the fifth interspace, and 7, 8 and 9, in the midline, 5 cm and 10 cm, respectively, to the left in the fifth interspace.

Q wave measured less than 2 mm. The term abnormal was used when a normal Q wave was present but the T wave was upright. Further—

3 Since this study was completed it has become the custom to reverse the polarity in taking lead IV, so the reader may need to look on the curves accompanying this article as opposite to those that are now being obtained (mirror image).



more, curves were regarded as indicative of myocardial infarction during the acute stage of the disease if the ST segment was decidedly elevated or depressed

#### FINDINGS FOR NORMAL HEARTS

A group of 55 young, normal, healthy nurses and house officers and 20 house patients who showed a normal condition of the heart at autopsy were studied. The patients examined post mortem died of conditions in no way related to the cardiovascular system. Analysis of the Q wave with each position showed that it was definitely deeper with the eighth and ninth positions than with any other position over the precordium and that the ninth position gave an average Q wave 1 mm deeper than that with the eighth position (table 1). In utilizing the presence or absence of the Q wave as indicative of myocardial infarction, the apical position is therefore preferable, because normally it is always determinable and there is the greatest excursion at this point.

It has been thought by some observers that a Q wave of less than 2 mm needs to be regarded with suspicion and is questionably indicative of myocardial infarction. This aspect was investigated in relation to the occurrence of a small Q wave in normal electrocardiograms. The frequency of a small Q wave in the electrocardiograms of 75 normal persons is shown in table 2. One can easily see that the chance placement of the electrode along or to the right of the sternum might have given a small Q wave or one questionably indicative of myocardial infarction in 5 to 20 per cent of these cases but that no such confusion would have resulted if the eighth or ninth position (or a position around the apex) had been used. For here a normal Q wave was always obtained. Since 9 chest leads were made for each of these 75 persons, 675 chest leads were studied. There were only 7 instances in which the Q wave was absent, and in each of these cases the electrode was placed over the base of the heart and not at the apex. Absence of the Q wave is therefore rare when the heart is normal.

In analyzing the form of the T wave obtained for these normal persons, a position was sought which normally would give an inverted wave, for an upright wave has been regarded as indicating a pathologic condition. It was found that with no position was the T wave invariably inverted. However, it was much more frequently upright with the first seven positions than with the eighth or ninth (table 2). It follows that the chance of obtaining an upright T wave when the electrode is placed along the sternum is great. In fact, with some leads, e g, from the right of the sternum, it appears to be normally upright rather than inverted. Several of these normal persons showed a definitely upright T wave with every precordial lead except the ninth, as illustrated in

TABLE 1—The Amplitude of the Q and T Waves with Various Precordial Leads

Condition	Number of Cases	Precordial Positions											Ape
		1	2	3	4	5	6	7	8	9			
Q Waves													
Normal (young persons)	55	18	5	18	18	36	10	5	0	0			
		07	1-10	1-8	111	1115	165	19	213	213			
		369	423	421	505	46	276	447	526	63			
Normal heart (autopsy)	20	25	30	20	15	15	45	15	0	0			
		0-55	0-7	0-45	18	111	18	05-15	212	220			
		236	294	31	364	41	196	383	505	709			
Mitral stenosis	10	50	40	40	40	40	40	40	30	0			
		05	07	08	0-10	08	06	09	15-12	3-12			
		31	35	42	507	42	273	492	592	682			
Syphills	5	80	80	80	80	60	60	80	60	40			
		02	025	02	025	03	0-1	025	045	09			
		06	08	06	08	11	04	08	19	32			
Hypertension	13	69	61	69	16	30	69	46	23	15			
		011	014	013	022	024	06	0-12	020	028			
		19	26	21	2	16	041	133	208	441			
Uremia	10	50	41	50	33	33	58	25	0	0			
		06	07	08	0511	15-9	04	17-5	211	29			
		19	275	26	383	4	166	29	433	16			
Subacute bacterial endocarditis	1	25	30	20	15	15	45	15	0	0			
		055	07	045	18	111	18	0515	212	220			
		236	294	364	364	11	196	383	505	709			
T Waves													
Normal (young persons)	55	67	41	43	16	10	76	25	9	18			
		5	35	15	1	6	15	1	15	15			
		4	7	15	12	2	9	135	95	10			
Normal heart (autopsy)	20	65	60	45	30	25	50	40	10	15			
		4	35	2	2	25	25	2	1	15			
		3	65	35	7	65	3	35	5	35			
Mitral stenosis	10	50	40	40	30	30	60	30	40	30			
		4	35	25	25	25	3	45	4	2			
		15	15	3	6	6	1	55	8	10			
Syphills	5	40	40	10	10	0	10	0	0	0			
		2	1	1	15	0	3	0	0	0			
		3	4	5	6	5	4	5	7	5			
Hypertension	13	46	46	53	38	40	69	38	15	0			
		35	3	45	25	3	25	5	25	0			
		15	4	35	45	6	6	10	95	12			
Uremia	10	40	40	40	30	60	40	20	30	50			
		5	4	6	3	2	5	5	3	3			
		5	5	4	4	4	4	8	7	7			
Subacute bacterial endocarditis	1	80	40	60	40	40	80	80	40	0			
		35	2	2	2	15	3	35	4	0			
		05	15	1	2	3	2	0	25	45			

figure 2 In only 4 cases was the T wave upright with every precordial position, and in these cases the lowest T wave was obtained with the apical position (figs 3 and 4) There is likelihood of finding an upright T wave with the apical position when the heart is normal, but it is small Besides the fact that the T wave was more frequently inverted with the apical position, the wave averaged about 1 mm deeper with this position than with any other precordial lead

In our study of 75 normal persons the Q wave was invariably present and was deeper with the apical position than with any other precordial position Likewise, the T wave, with rare exceptions, was inverted and deepest with the apical position Therefore, it seems reasonable to assume that if the criteria of myocardial infarction are the absence of the Q wave and the presence of an upright T wave, the apex is the point from which the chest lead should be obtained

TABLE 2—Frequency of Small Q Waves\* and Upright T Waves with Various Precordial Positions in Seventy-Five Cases in Which the Heart Was Normal

Precordial Position	Occurrence of Small Q Waves		Range of of All Q Waves, Mm	Occurrence of Upright T Waves	
	Number of Instances	Percentage		Number of Instances	Percentage
1	15	20	0-9	50	66
2	9	12	1-11	35	46
3	4	5	1-10	33	44
4	4	5	1-15	15	20
5	5	6	1-18.5	11	14
6	15	20	0.5-8	52	69
7	6	9	1-9	22	29
8	0	0	2-18.5	7	9
9	0	0	2-19	4	5

\* Less than 2 mm

#### EFFECT OF VARIOUS PHYSIOLOGIC AND PATHOLOGIC CONDITIONS ON THE PRECORDIAL LEADS FOR NORMAL PERSONS

*Respiration*—It has been observed that small variations in the depth of the Q wave may occur, and they seem to follow the respiratory cycle We therefore studied the effect of respiration on the fourth lead Tracings were taken for 2 normal young males during deep inspiration and in complete expiration with each of the nine positions With every position the Q wave was deeper during expiration than during inspiration The increase in the depth of the wave varied from 1 to 3.5 mm Five other normal young persons were observed during a complete respiratory cycle, which consisted of a deep inspiration that was held for several seconds and then complete expiration followed by normal breathing Inspiration shortened the Q wave in 4 instances and the T wave in 2 instances in the tracings obtained with the apical lead In 1 case the T wave went from 1.5 mm inverted to 1.5 mm upright, and the

Q wave changed from 4 to 1 mm in depth during held inspiration This curve could have been interpreted as questionably indicative of myocardial infarction during this period After expiration each tracing returned to its previous appearance This was most likely due to the

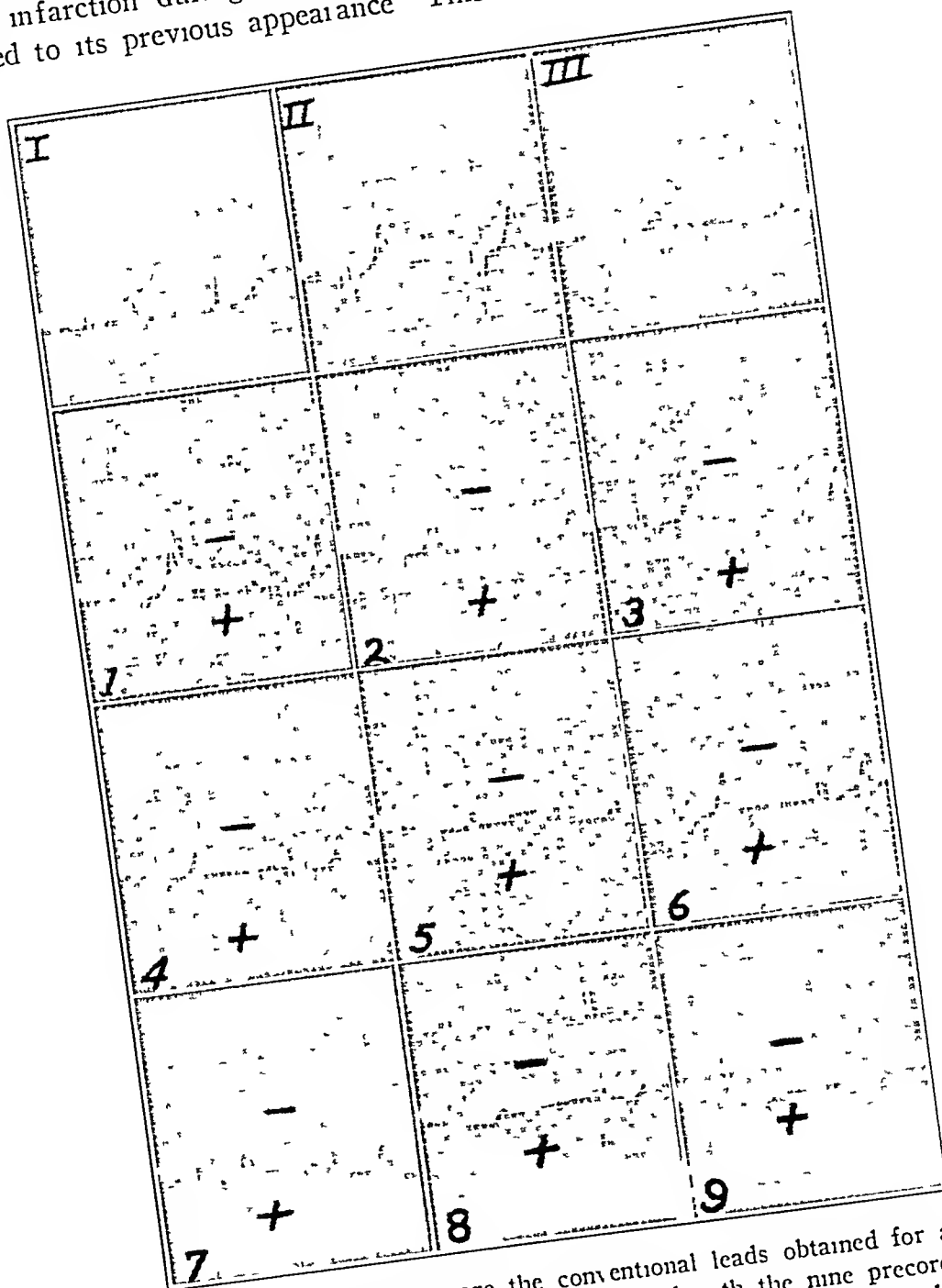


Fig 2—The first 3 curves are the conventional leads obtained for a normal person The remainder are the tracings obtained with the nine precordial positions Note the presence of an upright T wave in all leads except the last, taken from the apex

raising and lowering of the apex of the heart during marked respiratory motion In 2 cases in which there was an upright T wave with the apical

position, the height of the T wave increased during inspiration. One patient showed a Q wave only with the apical position, and there it varied from 0 to 2.5 mm and seemed to follow the respiratory cycle. The curves were interpreted as normal. This patient came to autopsy a few days later, and the heart, coronary arteries and myocardium were normal. It seems that more reliable information as to  $Q_1$  would be obtained if tracings were taken during normal breathing and certainly not during deep inspiration.

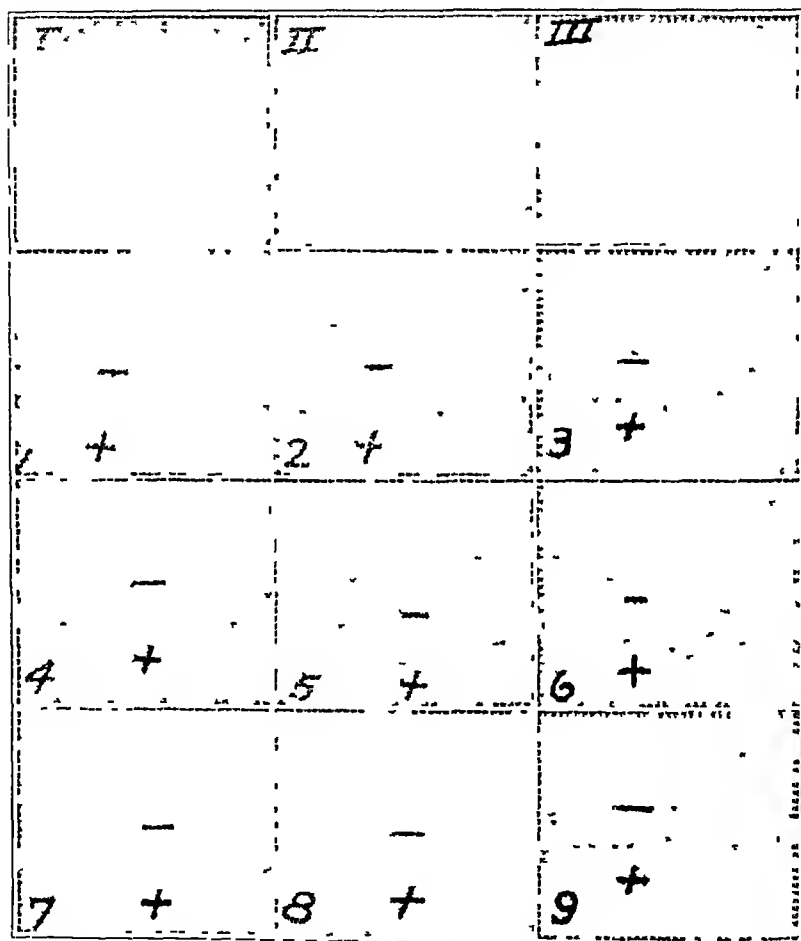


Fig 3—The first 3 curves are the conventional leads obtained for a normal person. The remainder are those obtained with the nine precordial positions. Note the presence of an upright T wave in all leads, the lowest being in the apical lead.

*Ice Water*—Tracings were taken for 2 normal young men just prior to and immediately after the drinking of 1,200 cc of ice water. The Q wave with the apical lead was definitely decreased, from 15 to 11 mm in 1 case and from 21 to 8 mm in another, after the ingestion of ice water. No significant changes were noted in the T wave.

*Position*—During this study it was necessary to make tracings for orthopneic patients while they were sitting down. In order to investigate the effect of posture, the nine chest positions were used for each of 5 young healthy persons while they were on the back and on the right and left side as well as in the sitting position. There were no significant

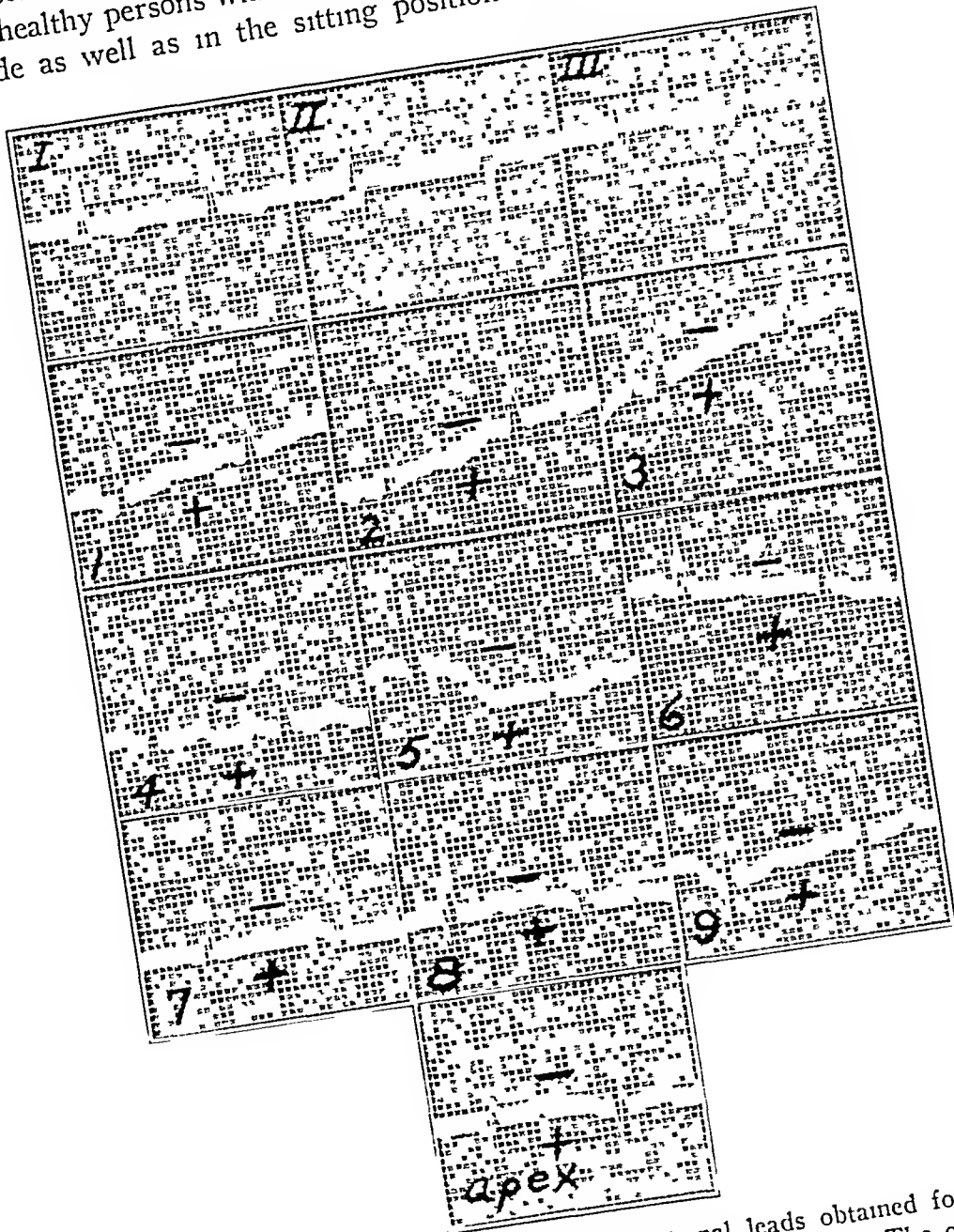


Fig 4—The first 3 curves are the conventional leads obtained for a patient who died of carcinomatosis. Autopsy showed a normal heart. The other curves are the precordial leads. Note the upright T waves in all the precordial leads.

changes in the tracings except in 2 instances, in which the upright elevation of the QRS entirely disappeared with an increase in the downward deflection. One of these tracings occurred when the subject was

changing from the right to the left lateral position and the other when he was changing from the prone to the sitting position. There were slight changes in the depth of the Q and T waves with the various positions, but the apical position gave a normal curve in each case, whether the patient was on his back, on his right or left side or sitting up. We believe that if the apical position is used, the value of the interpretation will remain constant, regardless of whether the patient is in the prone or the sitting position.

*Fluid in the Left Side of the Chest and Abdomen and Collapse of the Lung*—Curves were made for 6 patients before and after the removal of fluid, varying in amount from 250 to 2,000 cc, in order to determine the effect of fluid in the left pleural space on the precordial tracing. The Q and R waves with the apical position were definitely increased in each case after the removal of the fluid from the left pleural space. The greatest single increase in the Q wave was 11.5 mm after the removal of 2,000 cc of fluid. In 1 case curves were made with the apical position before and after removal of 2,000 cc of fluid, and it was found that there was no Q wave before thoracentesis and that there was a 7 mm Q wave after tapping. The response of the T wave was variable. If it was upright before thoracentesis, it might remain upright or become inverted. If it was inverted before thoracentesis, it might remain inverted or become upright. We believe that if fluid is present in the left pleural cavity the interpretation of the fourth lead should be held in reserve, as an absent or small Q wave may become normal after thoracentesis.

There were 2 patients with tuberculosis of the left lung, one of whom was treated by complete thoracoplasty on the left and the other by injection of oil into the pleural cavity. Each had complete collapse of the left lung. With many of the precordial leads the Q wave was less than 2 mm, but with the electrode at the apex it was normal in each case, and the T wave was inverted. One patient with spontaneous pneumothorax on the left side also had a normal fourth (apical) lead. Master and his associates<sup>4</sup> noted the complete absence of Q<sub>4</sub> in 2 cases of spontaneous pneumothorax, with return of the Q wave on absorption of the pneumothorax and reexpansion of the collapsed lung.

Removal of a large amount of abdominal fluid, e. g., 14,000 cc, has been observed to change a questionably positive Q wave before tapping to a normally deep Q wave (10 mm) after paracentesis. One patient who showed this sequence came to autopsy later and had a normal myocardium.

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<sup>4</sup> Master, A. M., Dack, S., Kalter, H. H., and Jaffe, H. L. The Significance of an Absent or a Small Initial Positive Deflection in the Precordial Lead, *Am Heart J* 14: 297, 1937.

*Pulmonary Conditions*—Precordial tracings taken for several patients with pneumonia of the lower lobe of the left lung were normal throughout. There were, however, 2 instances in which the Q wave was present only with the apical lead, being 4.5 and 1.5 mm, respectively.

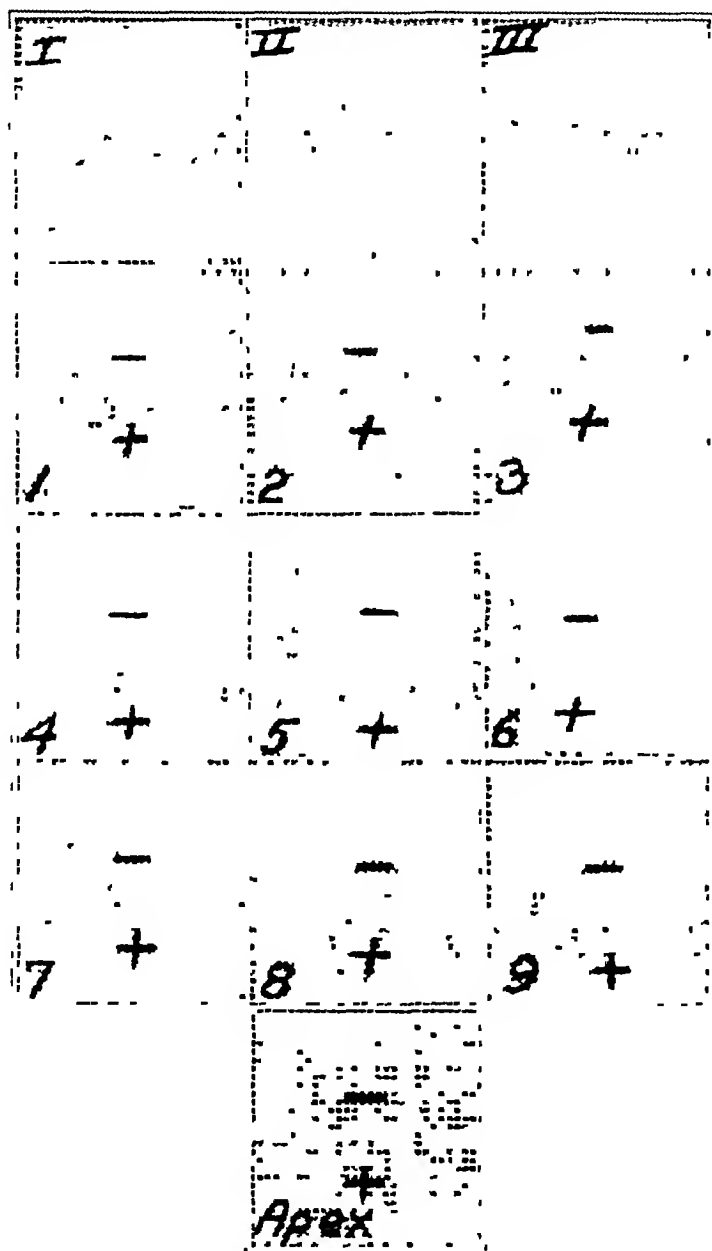


Fig 5—Tracings for a patient with pneumonia of the lower lobe of the left lung and aortic stenosis. Autopsy showed no myocardial infarction. Note the absence of a Q wave in all leads except the apical.

tively (fig 5). In the latter case the curve was interpreted as questionably indicative of myocardial infarction. Both patients were examined post mortem, and no cardiac infarction was present.

Four patients with pulmonary infarction of both the right and the left lung were studied prior to death. The Q wave was normal



with the apical lead in each case. The only abnormality noted was an upright T wave with a slightly high take-off in each precordial lead for a patient with an infarct of the middle lobe of the right lung. None of these 4 patients showed a myocardial infarct post mortem. One patient with bronchogenic carcinoma of the lower lobe of the left lung who at autopsy showed no heart disease had a normal Q and an upright T wave with each precordial position. Here, again, the tracing obtained with the apical position was the most reliable of all.

#### PATHOLOGIC HEARTS WITHOUT MYOCARDIAL INFARCTION

*Mitral Stenosis*—Ten patients with mitral stenosis were studied, 7 of them had regular rhythm, and 3 had auricular fibrillation. The latter 3 were examined post mortem and showed no disease of the coronary arteries or myocardial infarction. In none of the 10 cases was there any clinical evidence of angina pectoris. In the study of the various positions over the precordium, a small Q wave, of less than 2 mm, was found frequently (30 to 50 per cent) with all the positions except the apical. In all the cases the apical position gave a normal Q wave. There were 3 instances in which the Q wave might have been regarded as questionably indicative of myocardial infarction with all positions except the apical (fig. 6). An analysis of the form of the T wave showed it to be upright in 30 to 60 per cent of the cases with all positions, including the apical (table 1). However, the average depth of the T wave was greatest with the apical position. The T wave was upright throughout for 2 patients, one of whom was examined post mortem. Neither had angina clinically, and the patient who died had normal coronary arteries at autopsy.

It is interesting that the P wave in 3 of the cases of mitral stenosis was prominent and upright with nearly all the chest leads, more so when the electrode was near the base of the heart than when it was at the apex. It follows that in cases of mitral stenosis the alteration of the T wave is of practically no value in the diagnosis of myocardial infarction and the apical position must be used to interpret the significance of the Q wave.

*Syphilitic Heart Disease*—There were 4 patients with syphilitic heart disease in this series, all of whom were examined post mortem. The first had syphilitic aortitis with aortic insufficiency and died of congestive heart failure. The precordial electrocardiograms were entirely normal. A second had syphilitic aortitis and showed no Q wave except with the ninth and apical positions, when it measured 2 and 3 mm, respectively. The heart showed no narrowing of the coronary orifices, and the myocardium was normal. The 2 remaining patients had

definite narrowing of the coronary orifices but no coronary thrombosis or myocardial infarction. One of the 2 had definite angina pectoris for three years and showed considerable diffuse fibrosis of the myocardium. Neither of these patients showed a Q wave except in the

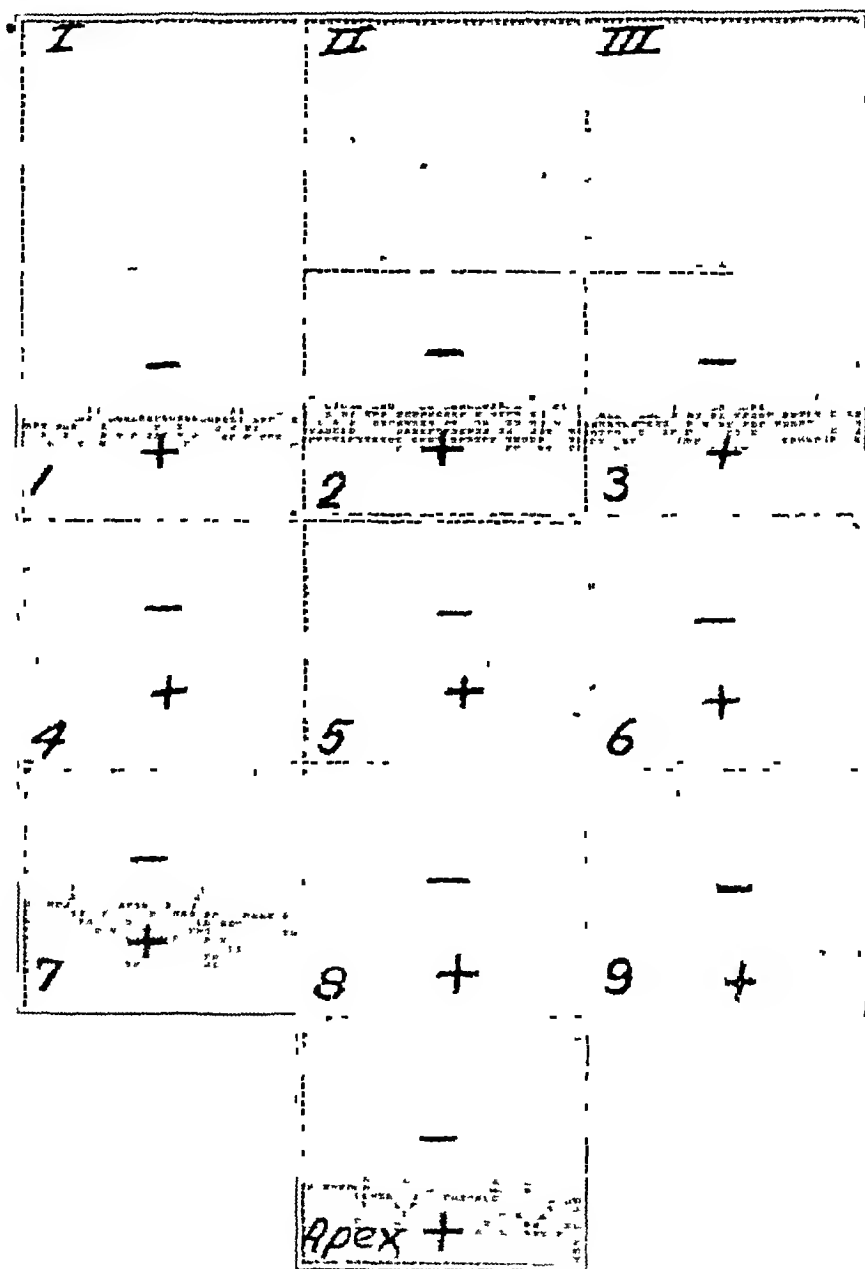


Fig 6—Tracings for a patient with mitral stenosis, auricular fibrillation and multiple pulmonary infarcts. Autopsy showed no myocardial infarction. Note that the Q wave is absent in all precordial leads except the ninth and apical leads.

apical lead, where it was only 0.5 mm (fig 7). One may conclude that syphilitic narrowing of the coronary orifices, without coronary thrombosis or myocardial infarction, may be associated with a small Q wave.

*Hypertensive Heart Disease*—This group included 13 patients, 7 of whom were examined post mortem. All had hypertension, and none had angina pectoris or a history of an acute coronary episode. Those studied post mortem did not have myocardial infarction. A small or questionably positive Q wave occurred frequently with the first eight

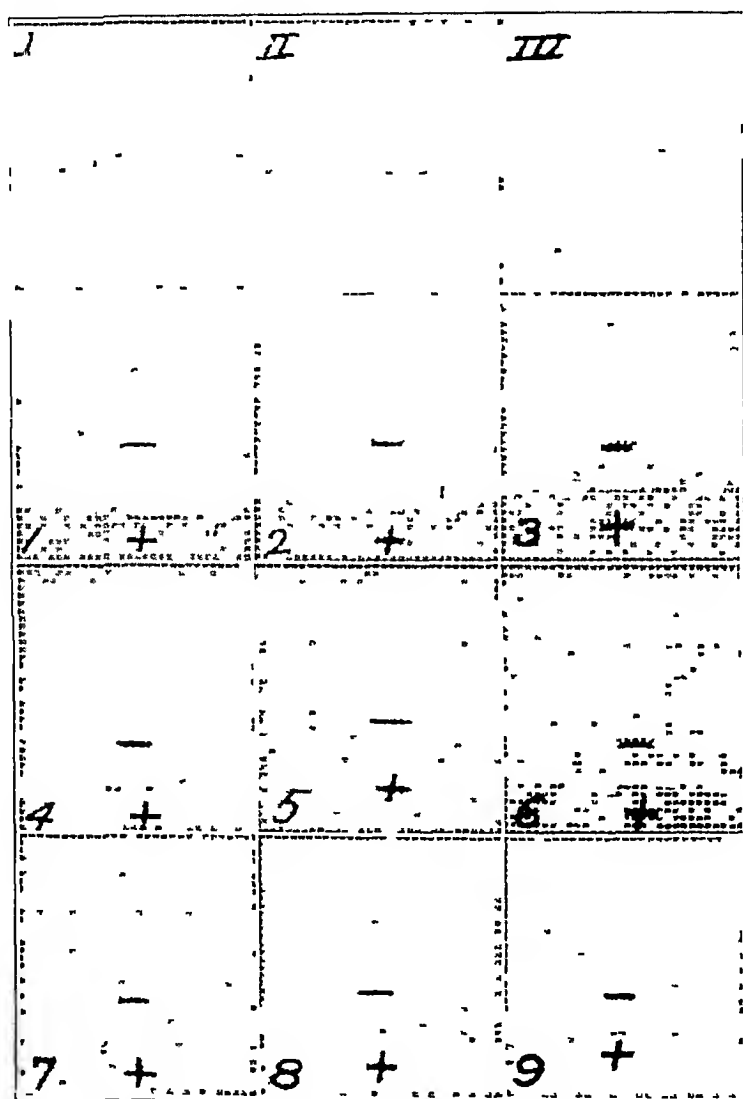


Fig 7—Tracings for a patient with syphilitic aortitis with angina pectoris. Autopsy showed marked narrowing of the coronary ostia without myocardial infarction. Note the absence of the Q wave except for a 0.5 mm wave in the apical lead.

positions over the precordium. The incidence of such small waves varied from 23 to 69 per cent with the different positions. With the ninth position, however, there were only 2 such cases, and with the apical position there were none. In fact, when the heart is enlarged

the Q wave with the apical position may be deep, and the change from a small to a prominent wave may take place abruptly with a change from the eighth or ninth position to the apical. In an especially interesting case (fig 8) there was an initial upward deflection before the Q

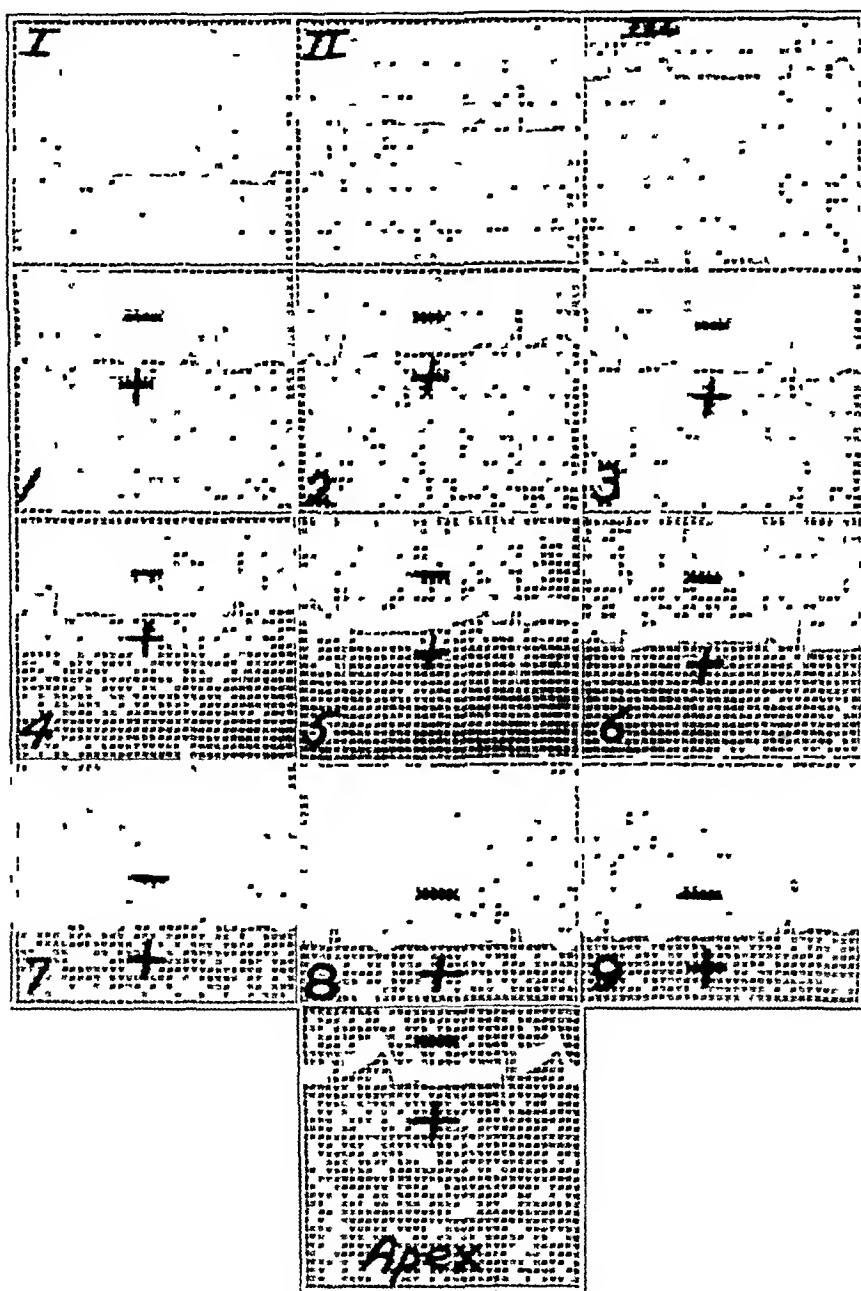


Fig 8—Curves for a patient who died of hypertensive heart failure. Autopsy showed no myocardial infarction or coronary thrombosis. Note that a small initial upright wave followed by a prominent downward wave does not indicate absence of the Q wave. The seventh, eighth and ninth leads show no Q wave, but a slight movement of the electrode toward the apex revealed a deep Q and an upright T wave.

wave of 3 or 4 mm in several of the precordial leads. In the seventh, eighth and ninth leads there was no Q wave, and the T wave was

inverted. Slight movement of the electrode toward the apex, however, produced after a slight upward deflection a Q wave of 26 mm and an upright T. Autopsy revealed no coronary thrombosis or infarction. It is significant that the slight initial upward deflection when followed by a prominent downward wave was not to be interpreted as indicating absence of the Q wave.

Analysis of the form of the T wave in these cases of hypertension showed that it was frequently upright (15 to 69 per cent) with the first eight positions, but in no instance was it upright with the ninth position. However, in 2 of the 13 cases, curves obtained from the apical impulse which was beyond the nipple line showed an upright T wave. These last 2 cases are important, because if the curves had been obtained only from the region of the nipple or midclavicular line they would have shown no Q and an inverted T wave and thereby would have been interpreted as indicative of infarction when none was present. It follows that, particularly when the heart is large, the precordial lead should be taken from the region of the apical impulse, for although the T wave may be upright the Q wave will be present. In fact, in many instances in which there is marked left axis deviation but no myocardial infarction, there are inverted  $T_1$  and upright  $T_3$  waves with the 3 conventional leads and a distinctly upright T wave with the apical position.

*Subacute Bacterial Endocarditis*—Our experience with 4 patients with subacute bacterial endocarditis who were examined post mortem was in accord with the general findings obtained when the heart is normal. The Q wave was either absent or small, and the T wave was upright in many of the leads except the apical. There was 1 instance in which the T wave was downward, and two months later, just a few days before death, it became upright with the first eight positions but was still inverted with the apical position. At autopsy there was a small mural thrombus in the posterior wall of the left ventricle which was an extension from the bacterial endocarditis of the mitral valve.

*Uremia*—There were 10 patients with uremia, 5 of whom were examined post mortem. Three of the 10 were under 25 years of age. Although there were frequent variations in the form of the Q and T waves with various precordial leads, the Q wave was invariably normal with the apical position, but the T wave was just as often upright as inverted. This group of patients showed the highest incidence of curves with an upright T wave with the apical position (50 per cent). The pericarditis so frequently associated with uremia seemed to have no effect on the direction of the T wave with the apical position. The T wave has been observed upright and inverted with the apical position in the curves for patients with and without pericarditis.

## DISTURBANCE IN THE MECHANISM OF THE HEART BEAT

*Auricular Fibrillation*—In cases of auricular fibrillation one often sees noticeable variation in the depth of the Q wave in successive beats. Also, the so-called f waves may distort the T wave so that it may appear upright in some complexes and diphasic or inverted in others. Furthermore, the depth of the T wave may vary in different cycles. Four persons with normal hearts who had transient periods of auricular fibrillation were studied. They each showed a normal fourth lead during both rhythms. The only variation was the altered depth of the Q and T waves in different cycles. There were 22 additional patients with fibrillation and various forms of heart disease, and 5 of them were studied post mortem. Each of the latter had a normal Q wave with the apical position, and none of them showed myocardial infarction. Of the remaining 17, 4 either had no Q wave or had a small one with the apical position, and in each instance there was a fairly satisfactory history of old or recent coronary thrombosis. The 13 other patients all showed a significant Q wave, and only 1 of them had a history of an acute coronary episode. In the latter case the changes in  $T_s$  were indicative of posterior infarction. It follows, therefore, that the presence of auricular fibrillation does not interfere with the correct interpretation of the fourth lead.

*Defective Intraventricular Conduction and Bundle Branch Block*—There were 23 patients in this group, 12 of whom were regarded as having delayed intraventricular conduction and 11 of whom showed the more classic electrocardiographic signs of left bundle branch block. Five of the former and 6 of the latter were examined post mortem. One of the patients with delayed intraventricular conduction who came to autopsy and showed anterior infarction had a Q wave of 0.5 mm in the apical lead and a markedly depressed ST segment. The 4 others had no infarction, and all showed a normal Q wave in the apical lead, although in many of the other precordial leads the Q wave was absent. There were 3 patients for whom the clinical evidence was adequate for the diagnosis of coronary thrombosis, and all showed complete absence of the Q wave in all the precordial leads. The interpretation of the presence or absence of myocardial infarction on the basis of the findings in lead IV was correct in all the cases of delayed intraventricular conduction.

The only difficulty that arose in the interpretation of the apical lead occurred for the group showing left bundle branch block. Of the 6 who were examined post mortem, 3 had anterior myocardial infarction, 1 of whom also had posterior infarction. In the last instance a Q wave, 1.4 mm deep, was obtained with the apical lead. It has been suggested<sup>4</sup> that the combination of anterior and posterior infarction may explain the presence of the Q wave in cases such as this. In the other 2 instances

of a proved anterior lesion, a Q wave with the apical lead was absent in 1 case and was 2 mm deep in the other. The 3 who showed no infarction had Q waves with the apical lead of 2, 3 and 4.5 mm, respectively. Of the 5 remaining patients with bundle branch block, 3 had clinical evidence of coronary thrombosis. One of these had a Q wave of 1 mm, another had a Q wave of 0.5 mm and the third had an M shaped complex extending 7 mm upward and downward. The last 2 patients had no clinical evidence of myocardial infarction and showed Q waves of 2 and 6 mm, respectively. The direction of the T wave shown by the group of patients with either delayed intraventricular conduction or bundle branch block was of no diagnostic aid, as it was found to be upright or inverted whether infarction was present or not. As a result of this analysis it may be stated that with occasional exceptions the same method of interpreting the apical lead applies when there is bundle branch block or normal intraventricular conduction.

#### COMMENT

Since the precordial lead first came into use there has been great variation in the technic employed by different investigators and in the opinions as to what position over the precordium gives the most useful findings. The technic originally described by Wolferth and Wood<sup>2</sup> was the use of the indifferent electrode in the interscapular region and the exploring electrode over the midprecordium. Since that time numerous reports have shown that it matters little where the indifferent electrode is placed, whether in the interscapular position or on the left leg. There has, however, been considerable disagreement as to the point of application of the exploring electrode. Some investigators have used two points for the exploring electrode—the left sternal border in the fourth interspace and the apex.<sup>5</sup> Others have used several points of application for the exploring electrode.<sup>6</sup> It now seems to be the consensus that the optimum point from which the chest lead should be taken is the apical impulse. Our results are in complete accord with this view. Bohning and Katz,<sup>7</sup> however, stated that the left sternal border in the fourth

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5 (a) Wood, F. C., Bellet, S., McMillan, T. M., and Wolferth, C. C. Electrocardiographic Study of Coronary Occlusion. Further Observations on the Use of Chest Leads, *Arch Int Med* **52** 752 (Nov.) 1933. (b) Levine, H. D., and Levine, S. A. An Electrocardiographic Study of Lead IV with Special Reference to the Findings in Angina Pectoris, *Am J M Sc* **191** 98, 1936. (c) Wolferth and Wood.<sup>2</sup>

6 Hoffman, A. M., and DeLong, E. Standardization of Chest Leads and Their Value in Coronary Thrombosis and Myocardial Damage, *Arch Int Med* **51** 947 (June) 1933. Master, Dack, Kalter and Jaffe.<sup>4</sup>

7 Bohning, A., and Katz, L. N. Four Lead Electrocardiogram in Cases of Recent Coronary Occlusion, *Arch Int Med* **61** 241 (Feb) 1938.

interspace is the best place to apply the electrode. They held this view because of the difficulty in finding the apical impulse in some cases. In this study the left sternal position in the fourth interspace was much less reliable than either the apex or the fifth interspace in the midclavicular line. In numerous instances patients without cardiac infarction at autopsy had no Q wave when the electrode was at the left fourth interspace and had a normal Q wave when it was at the apex. We believe that if the apical impulse cannot be definitely localized, the next most reliable information will be obtained by placing the electrode at the midclavicular line in the left fifth interspace. In our experience this position was unreliable in cases in which the heart was large and in which the apical impulse was easily located. In this regard, Master, Dack, Kalter and Jaffe<sup>4</sup> observed 3 patients with enlargement of the heart without myocardial infarction who had no Q wave in the precordial lead. The precordial position used by them was just inside the apical impulse. We have studied 5 similar cases in which there was no Q wave with any precordial position except directly over the apical impulse. Each patient had a Q wave of 2 mm or more with this position. All were examined at autopsy and had no myocardial infarction. It is suggested from this study that the exceptions recorded in the literature may be less frequent in the future if the electrode is placed over instead of inside the apical impulse.

Master, Jaffe and Dack<sup>8</sup> have also reported transient episodes in which the Q wave was absent during the course of acute glomerulonephritis, explained on the basis of diffuse capillary damage of the myocardium. As the process recedes the Q wave reappears. No studies were made of patients with acute nephritis in this investigation.

The significance of an upright T wave with the apical lead has been a point of controversy. Wolferth and Wood<sup>2</sup> said they considered this finding as indicative of coronary occlusion. Wood and his colleagues,<sup>5a</sup> Shipley and Hallaran<sup>9</sup> and Sorsky and Wood,<sup>10</sup> in studying large groups of normal persons, found no upright T wave with the apical lead. Master<sup>11</sup> and Edeiken, Wolferth and Wood<sup>12</sup> noted an upright T wave

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8 Master, A. M., Jaffe, H. L., and Dack, S. The Electrocardiogram in Acute Nephritis, *Am Heart J* **12** 244, 1936.

9 Shipley, R. A., and Hallaran, W. R. The Fourth-Lead Electrocardiogram in Two Hundred Normal Men and Women. *Am Heart J* **11** 325, 1936.

10 Sorsky, E., and Wood, P. The Use of Chest Leads in Clinical Electrocardiography, *Am Heart J* **13** 183, 1937.

11 Master, A. M. The Precordial Lead in One Hundred and Four Normal Adults, *Am Heart J* **9** 511, 1934.

12 Edeiken, J., Wolferth, C. C., and Wood, F. C. The Significance of an Upright or Diphasic T-Wave in Lead IV When It Is the Only Definite Abnormality in the Adult Electrocardiogram, *Am Heart J* **12** 666, 1936.



with the apical lead only rarely when cardiac infarction was not present. These investigators said they considered the presence of an upright T wave as definitely abnormal. Of this series of 75 persons with normal hearts, 4 showed an upright T wave with the apical lead. Three of these were proved to have normal hearts at autopsy. Of the 43 patients who had pathologic hearts without myocardial infarction, 12 showed an upright T wave with the apical lead. Nine of these came to autopsy and had no evidence of cardiac infarction. An upright T wave with the apical lead therefore occurs rarely when the heart is normal and not infrequently when the heart is pathologic without myocardial infarction. Other peculiarities in the form of the T wave with lead IV have been commented on. For instance, Katz and Kissin<sup>13</sup> stated that a T wave more than 9 mm deep should be regarded as abnormal. Sorsky and Wood<sup>10</sup> said they considered the deep T wave as normal. We have observed T waves as deep as 15 mm when the heart was normal (table 1). Digitalis has been shown by Strauss and Katz<sup>14</sup> and Stewart and Watson<sup>15</sup> to produce variable changes in the ST segment and T wave in lead IV. From this discussion it is obvious that there are several conditions that may alter the form of T<sub>4</sub> and that there is no general accord among investigators as to the significance of these variations. It is clear that a good deal of work must be carried out with respect to the conditions under which alterations of T<sub>4</sub> can occur. It is only in this way that the diagnosis of myocardial infarction can be further clarified.

#### SUMMARY

A study was made to ascertain which point over the precordium could be used in taking the so-called lead IV that would furnish the most reliable information in the diagnosis of myocardial infarction. For this purpose 9 or 10 tracings were taken with the electrode in various parts of the precordium in each of 352 cases. The two main criteria that were analyzed were the presence or absence of the Q wave and the direction of the T wave. In this study tracings were regarded as indicative of myocardial infarction if the Q wave was absent. They were called questionably indicative of infarction if the Q wave was less than 2 mm deep. The term abnormal was used when a normal Q wave was present but the T wave was upright. It was found that interpretations of the

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13 Katz, L. N., and Kissin, M. A Study of Lead IV. Its Appearance Normally in Myocardial Disease, and in Recent Coronary Occlusion, *Am Heart J* 8: 595, 1933.

14 Strauss, H., and Katz, L. N. Effect of Digitalis on the Appearance of Lead IV, *Am Heart J* 10: 546, 1935.

15 Stewart, H. J., and Watson, R. F. The Effect of Digitalis on the Form of the Human Electrocardiogram, with Special Reference to Changes Occurring in the Chest Lead, *Am Heart J* 15: 604, 1938.

electrocardiograms obtained with the electrode over the base of the heart and along the sternum were often misleading. The error decreased as the apical region was approached. It was also found that the electrocardiograms obtained with the electrode in the region of the nipple or in the midclavicular line, although generally reliable, were frequently not so when there was considerable cardiac hypertrophy. The only lead that gave a curve for which a satisfactory interpretation could be made with an extreme degree of accuracy was the one for which the electrode was placed over the apical impulse of the heart.

For 75 persons with normal hearts the Q wave was normally present and deepest with the apical lead. With the other positions it was often small (less than 2 mm) and rarely absent. The T wave was frequently upright with many of the precordial positions and in 4 instances even with the apical lead.

Deep inspiration was found to shorten the Q wave and to change an inverted to an upright T wave in some instances. More reliable information could be obtained during normal breathing than during deep inspiration.

Although minor differences in the electrocardiograms were noted with the patient in the supine, upright, left lateral or right lateral position, these did not alter the accuracy of the interpretations with the apical lead.

It was found that when fluid was present in the left pleural cavity, an absent or small Q wave might become normal after thoracentesis.

The removal of fluid from the abdomen changed a small Q wave to a normal one.

When the heart was considerably enlarged, owing to vascular disease, hypertension or other causes, frequently there was no Q wave with any of the precordial leads except the apical. The T wave was often upright even with the apical lead.

Two patients with syphilitic narrowing of the coronary ostia without myocardial infarction showed a Q wave of only 0.5 mm with the apical lead.

The presence of auricular fibrillation or delayed intraventricular conduction did not interfere with the correct interpretation of the fourth lead. In 2 of the 11 cases of left bundle branch block the method of interpretation of lead IV used in this study was incorrect.

It can be concluded that, except in the rare instances cited, a Q wave of 2 mm or more in the electrocardiogram with the apical position will always be found when the heart is normal or when there are various forms of heart disease unassociated with anterior myocardial infarction.

# THE PRECORDIAL LEAD

## II FINDINGS FOR PATIENTS WITH MYOCARDIAL INFARCTION

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In the preceding paper<sup>1</sup> the use of multiple points over the precordium in obtaining lead IV was discussed. In that paper the findings for patients with normal hearts and for those with various pathologic conditions of the heart and lungs other than myocardial infarction were reported.

A similar study has been made of patients suffering from, or suspected of having, myocardial infarction. The technic was the same as that used in our previous study, i e, nine designated points over the precordium were employed (see figure 1 in the first paper). If the apex was outside the ninth position an additional tracing was made with the electrode placed directly over the apex of the heart. The positions will be referred to in the future as leads IV<sub>1</sub>, IV<sub>2</sub>, IV<sub>3</sub>, etc. The customary German silver electrodes (1½ by 2 inches [3.8 by 5 cm]) were used. The exploring electrode was placed over the precordium with its long axis parallel to the long axis of the body. The indifferent electrode was placed on the left leg, the right arm electrode was used as the exploring electrode<sup>2</sup>. The normal tracing obtained by this method consists of an initial downward deflection of more than 2 mm (Q wave) and an upward R deflection and an inverted T wave. A tracing which has a normal Q wave of 2 mm or more but an upright T wave is considered as abnormal, the presence of a Q wave of less than 2 mm as questionably indicative of myocardial infarction and absence of the

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From the Medical Clinic of the Peter Bent Brigham Hospital

1 Robinson, R W, Contratto, A W, and Levine, S A. The Precordial Lead. I Findings for Patients with Normal Hearts and Those with Heart Disease Other Than Myocardial Infarction, Arch Int Med this issue, p 711

2 Since this study was completed it has become the custom to reverse the polarity in making lead IV, so that the reader will need to look on these curves as opposite to those that are now being obtained (mirror image)

Q wave as positive evidence of myocardial infarction Likewise a marked deviation of the ST segment from the isoelectric line is considered indicative of the acute stage of myocardial infarction

#### MATERIAL

Tracings were taken for 82 patients who had typical histories and clinical findings of cardiac infarction or who showed changes in the conventional leads which could be interpreted as indicative of cardiac infarction In 20 of these cases myocardial infarction was proved at autopsy Fifty-three of the patients were men, whose ages varied from 31 to 81 years, with an average age of 52.2, and 29 were women, the youngest being 48 and the oldest 87, with an average age of 64 In careful analysis of the tracings no significant differences were noted between those for men and those for women, therefore, no further detailed differentiation of the two sexes will be made Studies were also conducted on a group of patients who had histories suggestive of coronary thrombosis

During this study we had the opportunity of making tracings for several different groups of patients Twenty-eight of the patients, as far as could be determined, were suffering from a first attack of cardiac infarction The infarction was of the anterior type, and tracings were obtained within the first week of illness Sixteen additional patients were judged to have had only one healed myocardial infarction Electrocardiographic changes showed it to be of the anterior type, and the history suggested that it was at least six weeks old The time which elapsed between the acute episode and the making of the tracing varied from six weeks to twenty-five years The average interval was sixteen months, not including one unusual interval of twenty-five years Seven patients had acute myocardial infarction of the posterior type Thirty had multiple cardiac infarcts, and for 14 the diagnosis was verified at autopsy Some cases were also included in which the history, clinical findings and electrocardiographic tracings were suggestive but not typical of cardiac infarction

#### ACUTE ANTERIOR INFARCTION

For 28 patients who were suffering from acute anterior infarction, conventional electrocardiograms were made, together with tracings from the nine previously designated points over the precordium and from the apex of the heart if it was outside the position indicated Tracings were obtained for the majority of these patients within a day or two after the acute episode, and all had tracings taken within the first week of illness

For 6 of the 28 patients the first electrocardiograms showed no diagnostic evidence of cardiac infarction in the three conventional leads, while the tracings taken from the precordium were typical Subsequent conventional leads, however, showed changes in 3 cases which were typical of acute anterior infarction

*The Q Wave*—From the majority of these first precordial electrocardiograms the Q wave was absent However, it may not disappear for several hours or days after the acute episode In 1 of our cases in which

the clinical history and findings were typical of cardiac infarction and in which changes in the electrocardiograms were indicative of acute anterior infarction, there was a Q wave of 2.5 mm until the seventh day, when it was 1.5 mm, and it did not disappear entirely until fifteen days after the acute attack (fig 1). Another patient retained a small Q wave until the twenty-eighth day after the acute episode, when it disappeared. It seems, therefore, that although a Q wave is not found in the apical lead in most cases of anterior infarction, it may not disappear for a few weeks after the onset of the acute attack.

Electrocardiographic tracings taken from the nine positions over the precordium and from the apex showed no Q wave in the majority of these cases of acute cardiac infarction of the anterior type. In several cases a small Q wave, of less than 1.5 mm, was present with the first to ninth positions and absent with the apical position. In the occasional case a Q wave of less than 1 mm was present also in the apical lead. One patient, who showed clinically typical symptoms of acute myocardial infarction and at autopsy showed a recent large infarction of the anterior portion of the myocardium, had normal conventional leads and also a deep Q wave in the tracings taken from all the nine points over the precordium except the one taken from over the apex, which showed no Q wave (fig 2). In this case the apical lead was the only one from which a decisive electrocardiographic diagnosis could be made. Two other patients who had clinical coronary thrombosis and who also showed progressive changes in the conventional leads showed absence of the Q wave only in the eighth, ninth and apical leads. On the other hand, occasionally the conventional leads may be characteristic of anterior infarction when all the precordial leads are normal (fig 3).

In several cases tracings were taken from a point 3 cm outside the apical impulse. The majority of these tracings were of the same general type as those obtained elsewhere over the precordium. However, in some the Q wave, which was absent with the apical position, was prominent with the lead taken 3 cm lateral to the apex (fig 4). It follows that in the majority of cases of acute anterior infarction, tracings taken from any point over the precordium show no Q wave. In some cases a Q wave was absent only from the apical lead. Tracings taken to the left of the apical impulse were unreliable. This is further evidence of the reliability of the apical position in obtaining lead IV.

*The ST Segment in Acute Anterior Infarction*—Wolferth and Wood,<sup>3</sup> in their original article on lead IV, called attention to the depression of the ST segment in cases of acute cardiac infarction. In

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3 Wolferth, C. C., and Wood, F. C. Electrocardiographic Diagnosis of Coronary Occlusion by the Use of Chest Leads, *Am J M Sc* **183** 30, 1932.

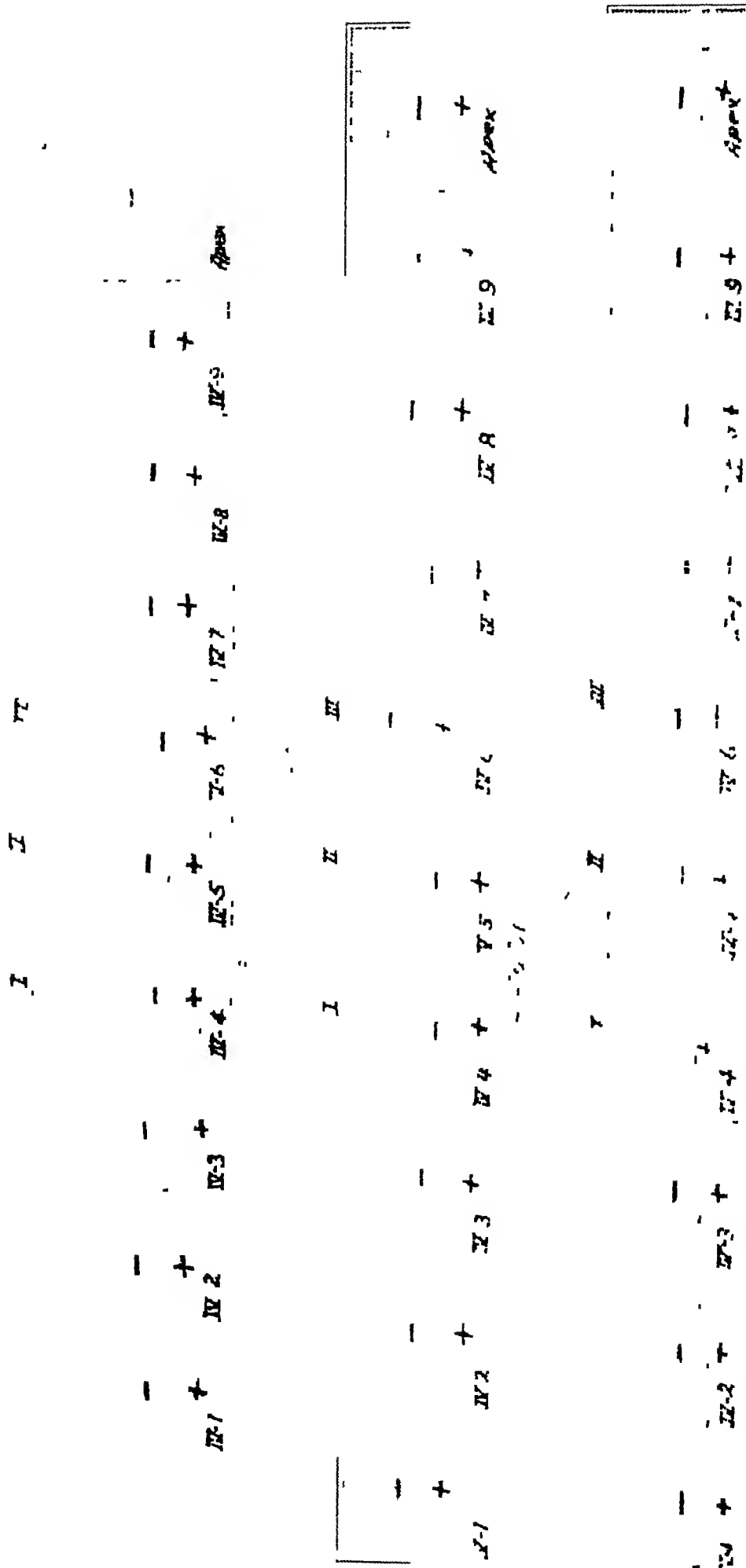


Fig 1—Note the progressive changes in the conventional leads. The tracings were made three, nine and thirteen days, respectively, after the acute attack. Note also the deeper ST segment and more marked changes in the apical leads than in other precordial leads and the progressive shortening of the Q wave in the apical leads.

the majority of cases of acute anterior infarction, depression of more than 3 mm of the ST segment is regarded as one of the most pathognomonic findings in tracings taken from the precordium. Rarely in the early hours or days after an acute infarction it may be the only positive electrocardiographic evidence in the conventional or precordial tracings. In our series 3 patients had as their only early change, depression of the

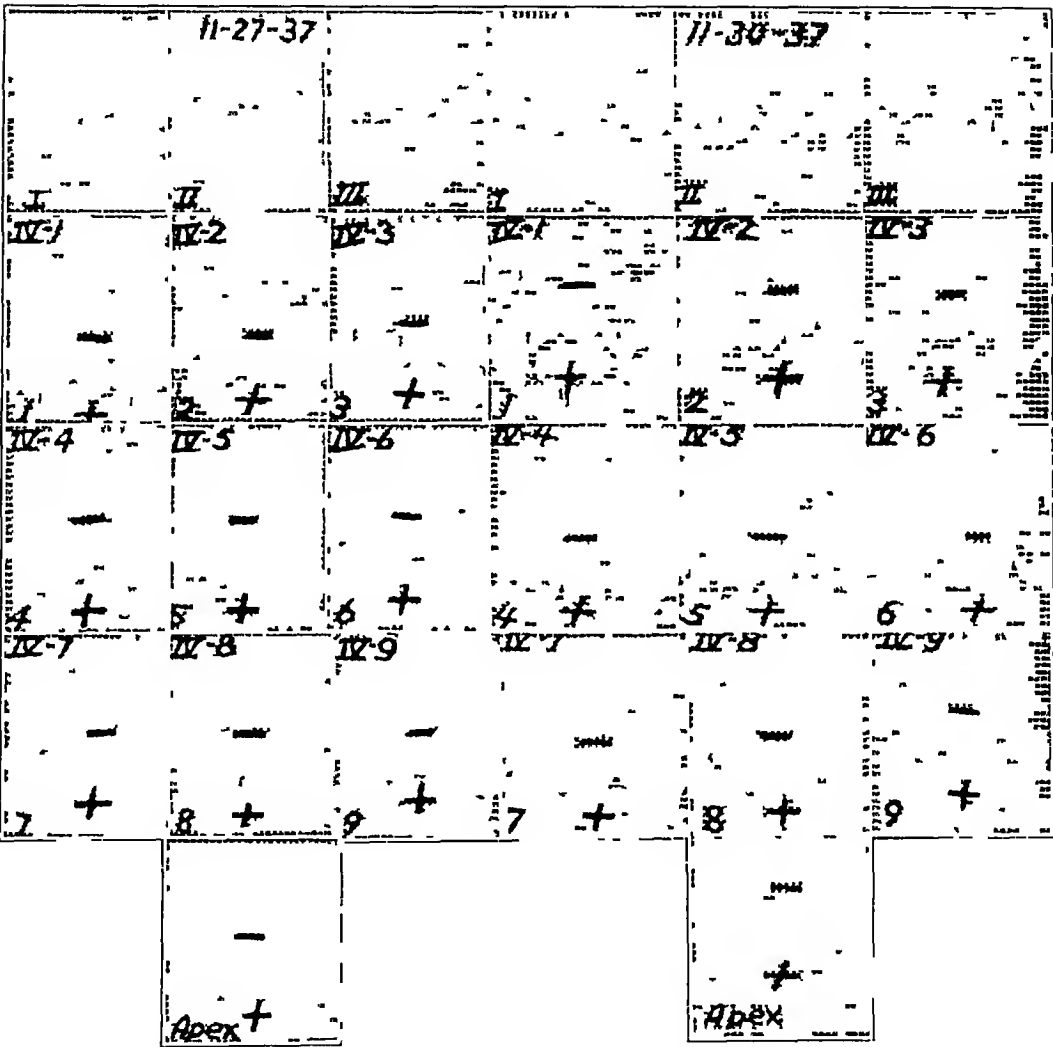


Fig 2—Note the absence of the Q wave only in the ninth and the apical lead, which was the only distinctive electrocardiographic evidence of anterior infarction shown in this case. At autopsy there was an acute anterior infarction. The tracings were made on the first and fourth days of illness.

ST segment in the precordial leads. This depression was present in practically all tracings taken from the precordium for every one of the 28 patients in this series. However, it was usually most prominent in tracings obtained from the apical region, in which the average depression

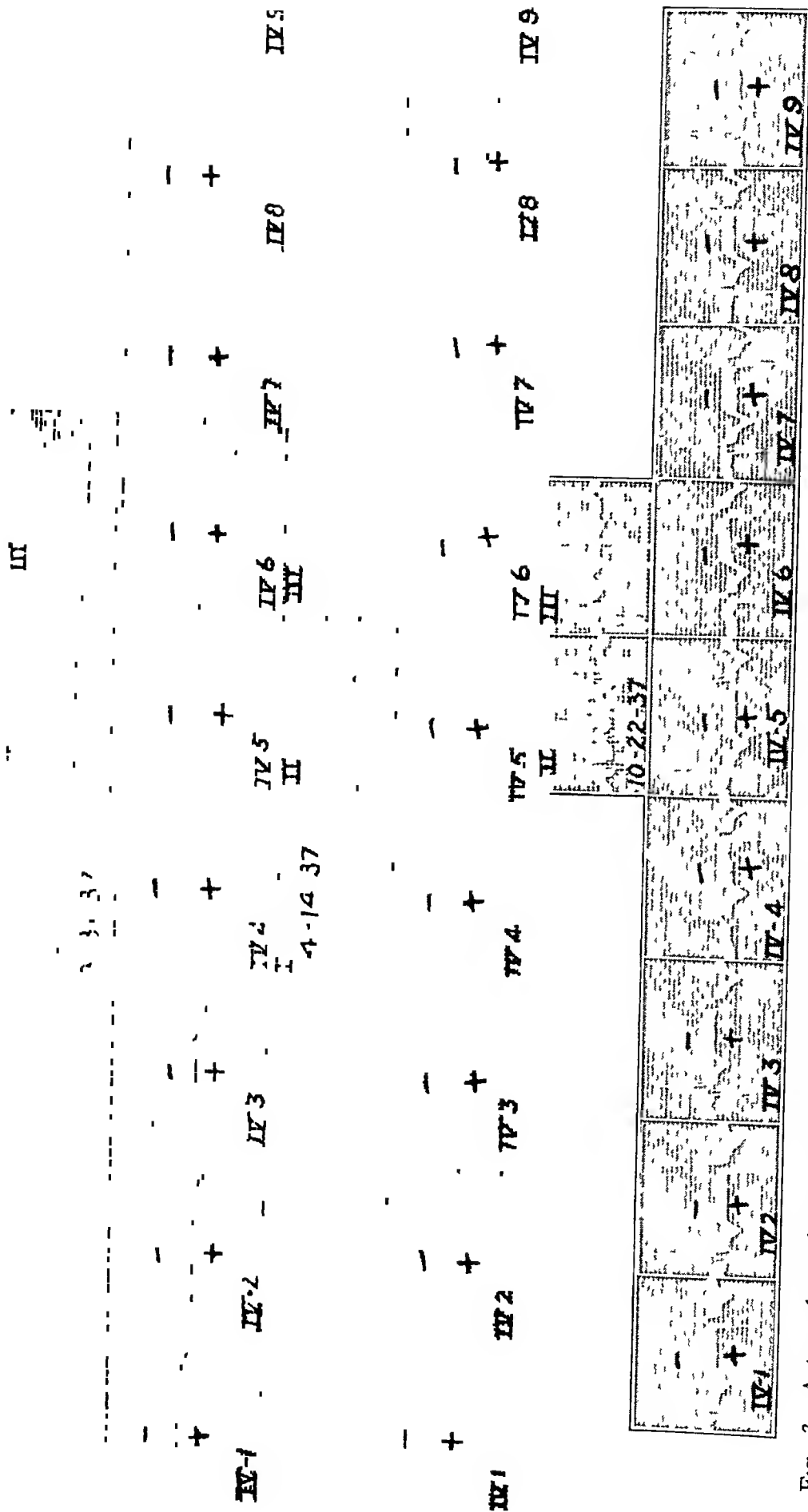


Fig 3—A typical attack of coronary thrombosis occurred on March 18, 1937 Note that the conventional leads indicate an anterior infarction, whereas all the precordial leads are normal



of the ST segment was about 4.3 mm, with extremes of 1.5 to 10 mm. With other positions it averaged as little as 1.8 mm (table 1).

In serial precordial tracings taken every other day for this group of patients it was noted that the most rapid changes were in the ST segment. It was generally deepest during the first day and gradually

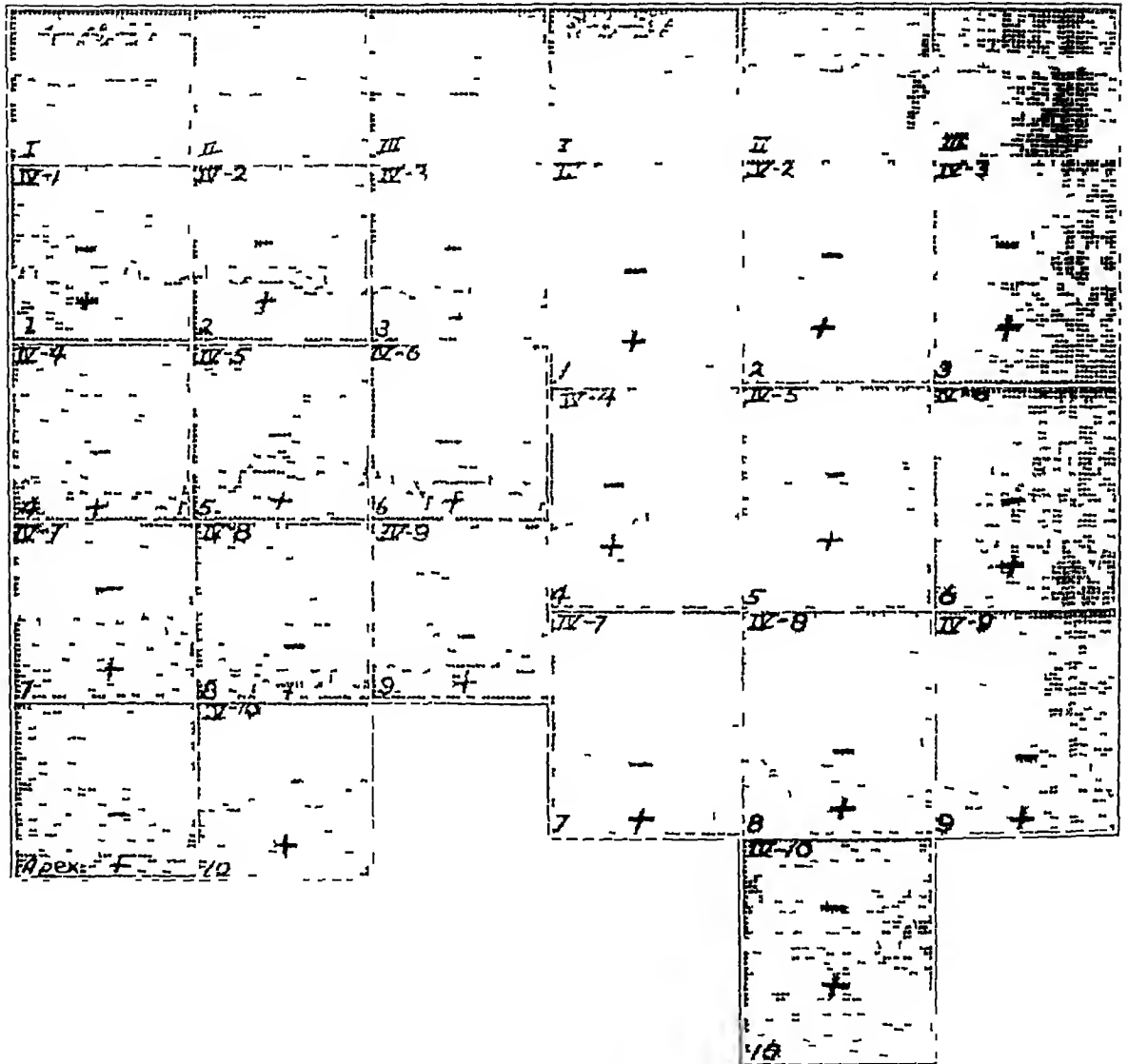


Fig 4—Note the absence of a Q wave in the ninth precordial and apical leads, which is indicative of anterior infarction, but the appearance of a large Q wave in the tenth lead, taken 3 cm outside the apex.

returned to the isoelectric line during the course of seven to fourteen days. The T wave became progressively more upright during this interval. In 1 case this change from a depressed ST segment to an upright T wave took place in as short a time as four days, while in

another it took place twenty days after the acute episode (fig 5) It was also noted in many cases that this change in the ST segment, with the T wave becoming progressively positive, took place much more rapidly in the tracings taken from the apical region, and no decisive change of the ST segment appeared in tracings from other parts of the precordium made during the six weeks of observation (fig 6)

One may conclude that if the criterion of a depressed ST segment which progressively changes to an upright T wave is to be used in the diagnosis of acute anterior infarction, as this evidence is more pro-

TABLE 1—*Depression of the ST Segment in Leads from Various Points Over the Precordium in Cases of Acute Anterior Infarction\**

Patient	Precordial Position									
	1	2	3	4	5	6	7	8	9	Apex
1	0	1	0.5	1.5	2	0	0.5	2.5	2.5	1.5
2	1.5	2.5	1.5	2.5	2.5	1.5	1.5	2.5	2.5	2
3	0	0	0.5	2.5	2.5	1.5	0.5	2	2.5	3
4	0.5	0.5	1	1.5	2	0.5	1.5	2.5	2	2
5	2	2	0.7	2.5	2	1.5	1.5	1.5	2.5	2.5
6	0	1	5	1.5	2	0	0.5	2.5	2.5	1.5
7	0	0	0.5	2.5	2.5	1.5	0.5	2	2.5	3
8	2	2	0.7	2.5	2	1.5	1.5	1.5	2.5	2.5
9	1	1	1	1	1	1	2	6	8	8
10	1	2	2	3	4	2	2.5	5	4.5	5
11	1	1	0	1	1.5	1.5	1.5	2	2	2
12	0.5	1	2	1.5	2	2	3	2.5	2	2
13	0	0	0	0	0	0	0	2	3	3
14	3	2.5	2.5	4	3	2	3.5	4	3.5	3.5
15	5	5	4.5	5	5	2	5	5	7.5	6
16	2	2	2	3	4	2	8	12	9	9
17	2	3	4	6	6	3	4	5.5	6	6
18	0	2	3	4	4	2	3	5	6	5
19	0	0	3	4	5	0	3	5	6	6
20	4	3	0	4	4	2	2	4	4	4
21	1	1	1	2.5	2.5	0.5	2	2.5	3	3
22	2	3	5	5	5	0	2.5	4	4	4
23	7	8	7	10	10	5	6	8	9	10
24	5	5	4.5	5	5	2	5	5	7	6
25	0	0	0	0	0	0	0	2	3	3
26	0.5	1	2	1.5	2	2	5	2.5	2	2
27	1	2	2	3	4	2	2.5	5	4.5	5
28	1	1	1	1	1	1	2	6	8	8
Average	1.5	1.8	2	2.9	3	1.4	2.5	3.5	4.3	3.9

\* The measurements are given in millimeters

nounced in tracings taken from over the apex than in those from other points in the precordium, the apical region is the optimal position from which the fourth lead should be taken

#### PATIENTS WITH ONLY ONE INFARCT OF SIX WEEKS' OR MORE DURATION

Tracings were taken for 16 patients who, as far as could be determined from the history, clinical findings and electrocardiograms, had had only one previous cardiac infarction, which was at least six weeks old. The interval between the occurrence of the infarction and the making of the first electrocardiogram varied from six weeks to twenty-five years

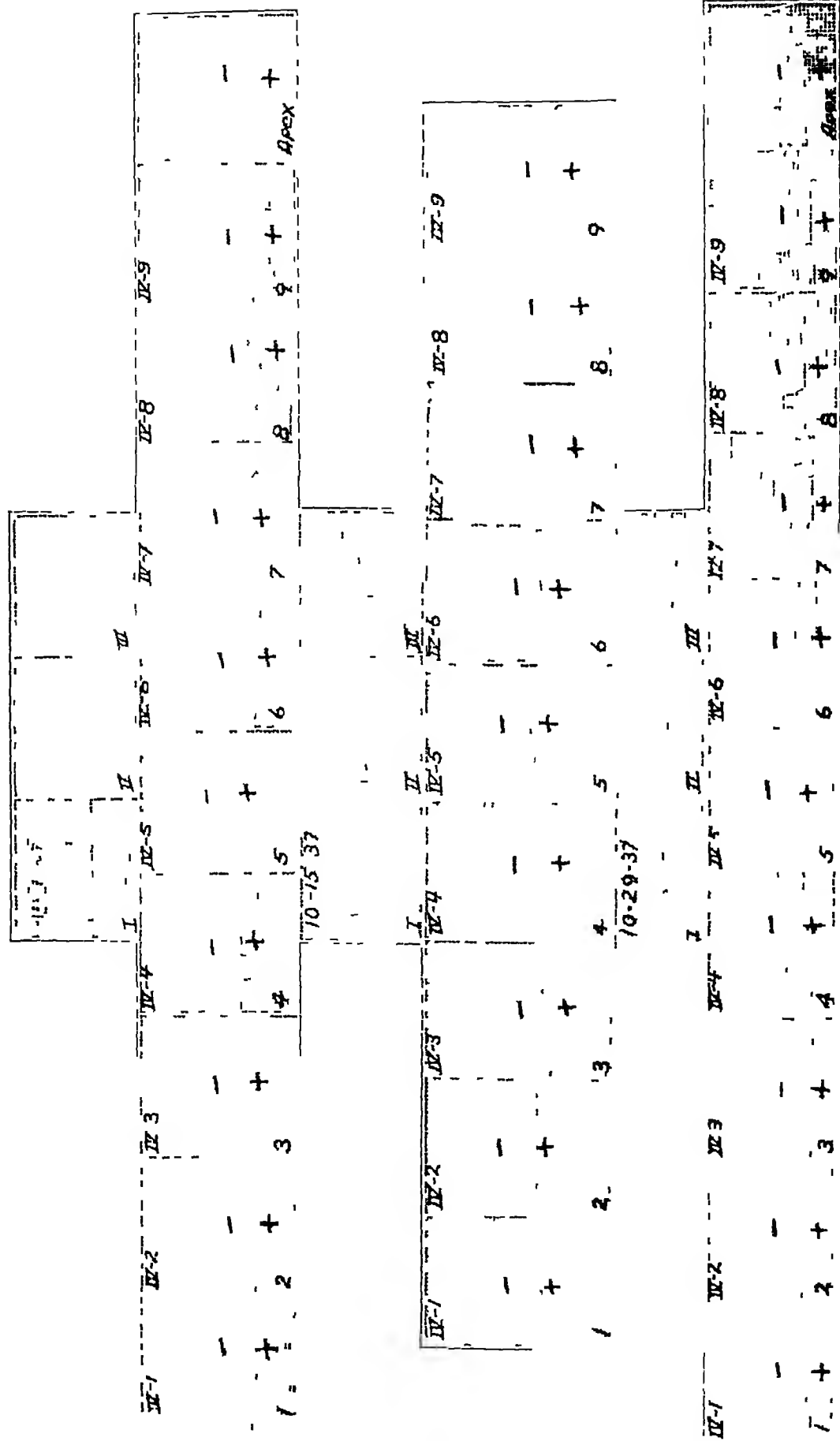


Fig 5—The acute attack occurred on Oct 9, 1937. Note that the conventional leads were not distinctive until three weeks later. The depressed ST segment in the precordial leads, especially in the apical lead, ending in an upright T wave, was fairly indicative of the diagnosis.

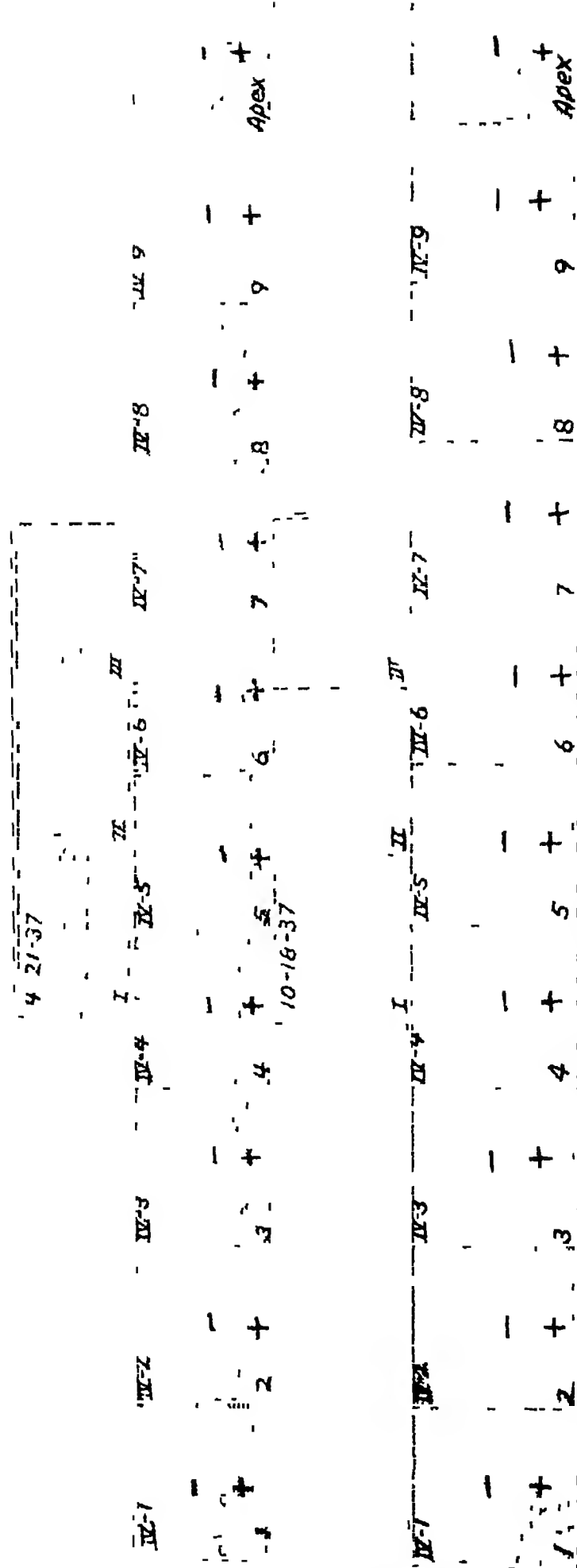


Fig 6—The acute attack occurred on April 5, 1937 Note that there was an upright T wave only in the ninth and apical leads

The average interval, not including the unusual period of twenty-five years, was five and seven-tenths months

For 9 of these patients the conventional tracings were normal except for left axis deviation in 2 instances. In the conventional tracings for the remaining 7 patients, evidence of distinct myocardial pathologic involvement was present. Tracings taken from the apical region showed no Q wave in any instance, while curves from other parts of the precordium showed a small Q wave, from 1.2 to 2 mm in several cases. In 10 cases the T wave was upright in the apical lead, varying from 0.5 to 9 mm, with an average of 4.5 mm. In 3 cases the T wave was inverted in the apical lead, ranging from 2 to 3 mm, and in 2 the T wave was isoelectric (table 2).

In the study of this group it was noted that in no case was a Q wave present in tracings taken from the apical position, while the T wave was upright in only two thirds of the cases. It follows that in the electrocardiographic diagnosis of cases of old single anterior myocardial infarction, the absence of the Q wave in the apical lead is more reliable than the presence of an upright T wave. It also adds further proof to the fact that when there are healed anterior infarcts the only positive electrocardiographic evidence in many cases may be obtained from the fourth lead.

#### PATIENTS WITH MULTIPLE INFARCTIONS

This group comprised 30 patients, many of whom, we were certain from clinical evidence, had had multiple infarctions. Others had had severe angina with more than one questionable infarction at some time during their illness. Still others showed evidence of multiple infarctions at autopsy.

The tracings for this series of patients were the most difficult to interpret. There were 4 cases in which the Q wave was rare in the various precordial leads except the apical, in which the main deflection was downward. Two of these patients came to autopsy, 1 had an acute posterior infarction (and a suggestive old anterior infarction), and the other had multiple old and recent infarctions of both the anterior and the posterior type. The conventional leads in the first case showed auricular flutter. In the other, bundle branch block was present. The 2 remaining patients were not examined post mortem. One had severe angina for ten years and several attacks suggestive of cardiac infarction. The conventional leads in this case were suggestive of an old infarction (fig 7). The other patient also had severe angina and showed typical clinical evidence of cardiac infarction. Our experience in these 4 cases in which the entire initial ventricular deflection was downward with the apical lead, although with most of the other precordial positions there was no Q

TABLE 2—T<sub>racings</sub> Taken from the Various Precordial Positions for Patients with Anterior Infarction of Six Weeks or More

Patient	Information Obtained from Conventional Leads	Q Wave (Lead IV), Mm												ST Segment Depressed, Mm												T Wave, Mm *												Time Since Acute Episode
		Q Wave (Lead IV), Mm												ST Segment Depressed, Mm												T Wave, Mm *												
		1	2	3	4	5	6	7	8	9	Apx	1	2	3	4	5	6	7	8	9	Apx	1	2	3	4	5	6	7	8	9	Apx							
1	Positive	0	0	0	0	0	0	0	0	0	0	2	3	2	3	3	1.5	2	2.5	2.5	3	u2	u3	u3	u4	u1.5	u2	u2.5	u4.5	u5	u7	6 wk						
2	Negative	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	u3	u3	u3	u3	u3	u2	u3	u1.5	u1.5	u5	2 mo						
3	Positive	0	0	0	0	0	0	0	0	0	0	0	1	2	2	3	3	2.5	3.5	3.5	0	u2	u5	u6	u6	u7	u5	u5	u7	u8.5	u6	4 mo						
4	Positive	1	0.5	0.3	0.5	0.5	0.5	0.5	0.5	0.5	0	1	1	1	1	1	1	1	2	1.5	1.5	du	du	du	du	du	du	du	du	du	du	u5	3 mo					
5	Positive	4.5	3	0.5	0	2	1.5	0	0	0	0	0	0	0	0.5	1	0	0	2	3	3	u1	u4	u1	u5	u6	0	u1	u5	u5.5	u9	5 mo						
6	Positive	0	0	0	0	0	0	0	0	0	0	1	1	2	3	3	3	3	3	2	2	u3	u3	u2	u3	u4	u4	u1.5	u3	u4.5	u5	15 mo						
7	Negative	3	2.5	2	1.5	1	1.5	1	0.5	0	0	0	0	0	0	0	0	0	1	2	2	0	0	0	u5	u5	0	u1.5	u2	u2.5	u3	2 mo						
8	Positive	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	u5	u6	u5.5	u6	u5.5	u5	u5	u6	u9	8 mo							
9	Negative	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	u4	u5	u4	u8	u7	u2	u4	u8	u7	u7	6 wk						
10	Negative	1	1	1	0.5	1.5	1.5	0.5	0.5	0	1.5	2	0	2	2	1	2	3	3	2.5	2.5	d2	d3	d4	d2	d1.5	d4	d4	d2	d2	d3	2 mo						
11	Negative	0.5	1	1.5	1.5	2	2	2	0.5	0	0	0	0	0	0	0	0	0	0	0	0	u2	u3	u2	u2.5	u3	u3	u2	u3	u3	u3	4 mo						
12	Negative	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	u1.5	u1.5	u2	u1	0	u1	du	0	0	0	5 mo						
13	Negative	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	0	2	1	2	2	d1	d1.5	d1	d1.5	d5	d2	d3	d3	d3	d3	2 yr						
14	Positive										0									0										du	25 yr +							
15	Negative	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	d1	u2	u2	du	du	du	d1.5	d3	d2	d2	4 yr						
16	Negative	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	u3	u2.5	u2.5	u1.5	u5	u1.5	u1.5	du	0	0	3 yr						

\* u indicates upright, d, inverted, du, diphasic, 0, isoelectric

† Only apical tracings were obtained

wave, suggests that when such a downward wave is found with the apical lead, multiple leads should be taken from other parts of the precordium. When most of these do not show a Q wave, one may regard this as presumptive evidence of myocardial infarction.

We had the opportunity of obtaining tracings for 2 patients who were observed during the acute stage of two separate attacks of coronary

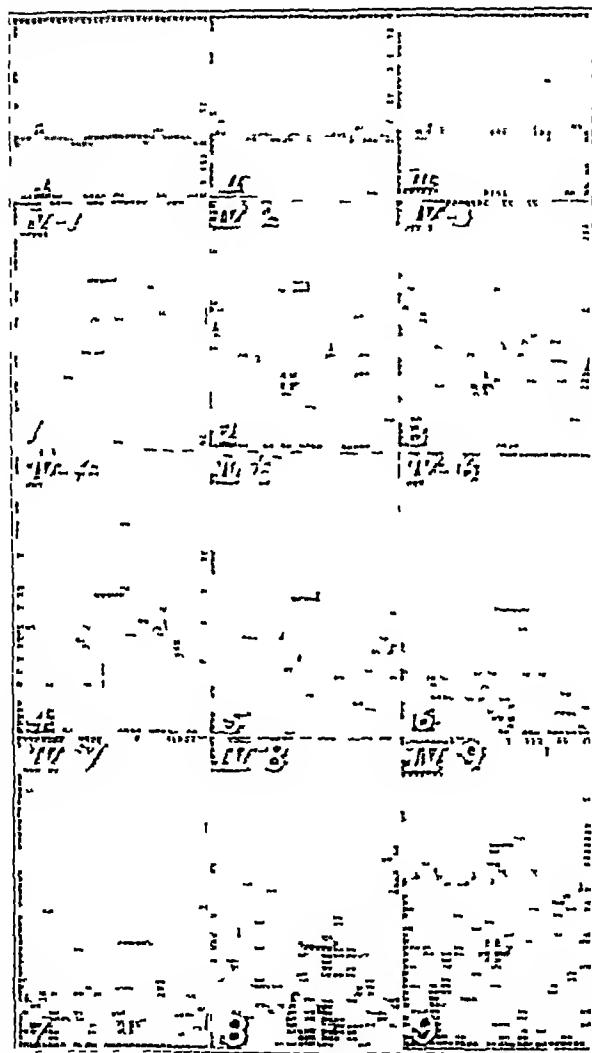


Fig 7—The patient had had severe angina for ten years. The electrocardiograms were suggestive of infarction nine months and three months before these tracings were made. Note that the conventional leads are suggestive, the Q wave is absent from every precordial lead except the apical, where the entire complex is downward.

thrombosis. In the first case the attack of posterior infarction occurred almost ten years after recovery from an anterior infarction (fig 8). It is interesting that the Q wave with the apical lead was still absent so many



Fig 8—An attack occurred on Jan 19, 1928. The early curves indicated the presence of an anterior infarction. Note that even ten years later there was no Q wave in the apical tracings.



years after the anterior infarction. The evidence of the new posterior lesion was apparent in the three conventional leads. In the second case a typical attack due to anterior infarction occurred, with recovery. This was followed six months later by another attack due to anterior infarction, and at this time the ST interval was again depressed (fig 9). The first anterior lesion, though healed, did not prevent the appearance of evidence of a fresh similar lesion.

In analyzing the remaining 24 cases we found that the conventional leads were normal in 7 cases, bundle branch block was present in 5, a low electromotive force, in 2, auricular fibrillation, in 2, auricular flutter, in 1, defective intraventricular conduction, in 1, and curves indicative of old anterior infarction, in 6. In none of these cases was there a Q wave of more than 1.5 mm in tracings taken from the apical position. In 15 instances the Q wave was absent from tracings with all positions over the precordium. In 5 the Q wave was absent only with the apical position, while tracings from other parts of the precordium showed a Q wave of 1 or 2 mm. In 8 cases there was a Q wave of 1 mm or less with the apical lead and of 2 mm or less with leads from other points over the precordium. In 2 cases a small Q wave, of 1 mm, was present with the apical lead and was absent with leads from other points over the precordium. Moreover, in none of the cases in which autopsy was performed was there a Q wave of more than 2 mm in the apical lead, with the exception of the 2 instances previously mentioned in which the entire deflection of the QRS complex was downward. The direction of the T wave was too variable to be of diagnostic aid in these cases of multiple infarctions.

#### SERIAL TRACINGS FOR PATIENTS WITH ACUTE ANTERIOR INFARCTION

Tracings were taken for 17 patients with acute anterior infarction every two or three days for a period of four to five weeks, and for some the tracings were taken six weeks to two years after the acute attack. No patient, as far as is known, had an attack of coronary thrombosis in the interim.

For 10 of this group the conventional leads were characteristic of acute anterior infarction at the time the original electrocardiograms were taken. In 3 cases the conventional leads were suggestive, and in 3 they were normal. Subsequent conventional leads for those with suggestive tracings showed definitely positive evidence in three to six days. In only 2 cases did the conventional leads return to normal while the patient was under observation (seven and sixteen months, respectively) after they had shown definitely positive evidence. In 2 cases the curves became suggestive but not definitely indicative of coronary thrombosis. In 3 instances in which the conventional leads were suggestive, these leads

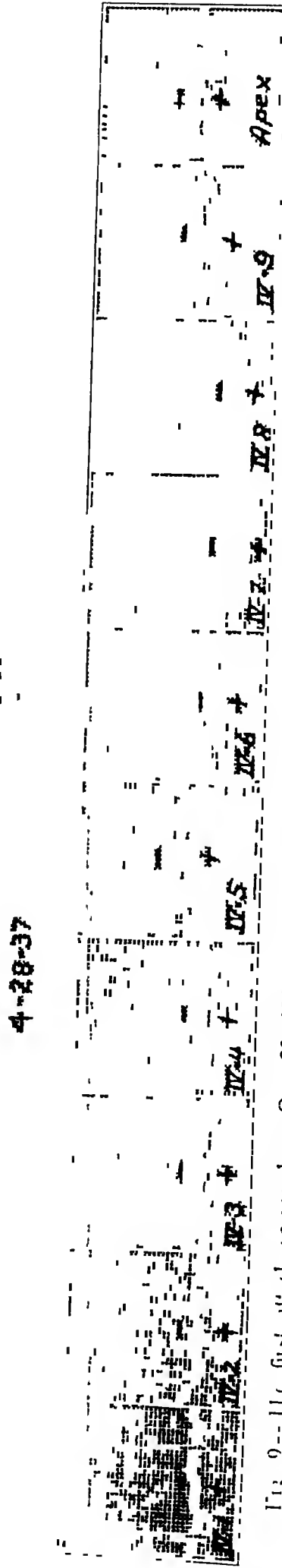
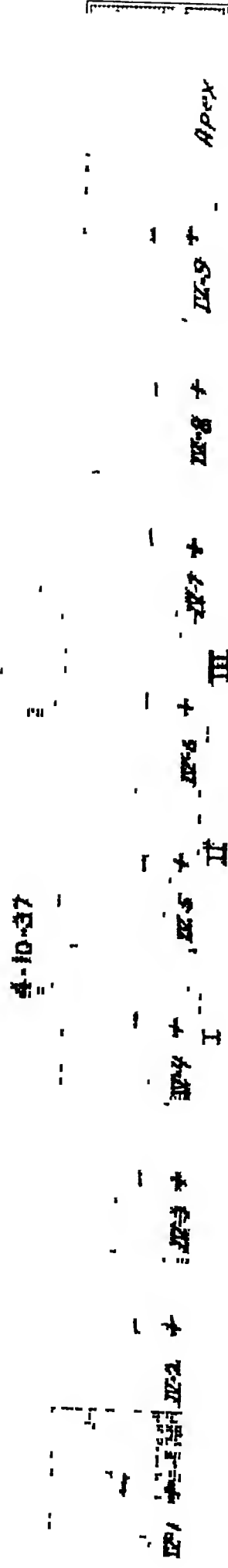


Fig. 9--11. First attack occurred on Oct 20, 1936. Conventional and precordial leads were made on October 23, all were typical of acute anterior infarction. Tracings were made on April 10, 1937, while the patient was having anginal attacks, note the residual evidence (absent Q<sub>1</sub>) of an old anterior lesion. A second attack of thrombosis occurred on April 24, 1937. Note that four days later the RT segment was noticeably depressed in the apical lead.

reverted to normal in one to two months. Subsequent electrocardiograms taken for these patients twenty-one months after the acute stage still showed normal conventional tracings.

*The Precordial Q Wave*—In 1 case the Q wave remained normal throughout the period of observation (fig 3). For the remaining group it was absent with the apical position in every case. With some of the other positions a small Q wave, of less than 2 mm, was present in some instances. In the serial follow-up tracings for these patients, the Q wave remained absent in 14 cases, while in 2 it returned to a depth of 0.5 and 1 mm, respectively. In another case it returned to a depth of 2 mm in the apical lead. At autopsy this patient had an old left anterior descending and an acute posterior thrombosis. This is the only case in which the Q wave returned to an extent which would be considered normal in the apical lead, although a more prominent Q wave reappeared with other positions over the precordium.

*The Precordial T Wave*—In serial tracings the T wave became upright during the acute stage in 11 of the 17 cases. This change, as previously mentioned, occurred most rapidly in the apical lead. In the majority of instances the T wave reached its greatest upward deflection on about the tenth to the fourteenth day after the acute episode and then receded to a fixed point, but it remained upright to a certain degree during the period of observation. In 8 of these cases it remained upright for periods up to two years. However, in 3 cases it went through the progressive changes from a depressed ST segment to an upright T wave and during the period of observation became inverted again. In 6 cases the T wave never was upright during the period of observation.

*Comment*—It follows that the most constant change in the precordial leads for this group of patients was the absence of the Q wave from tracings taken from the apical region. Likewise, in serial tracings the Q wave did not return to a size of more than 2 mm in any case while the patient was under observation. In contrast, the changes in the T wave were variable and less reliable.

#### ACUTE POSTERIOR MYOCARDIAL INFARCTION

In our experience acute posterior infarction was much less common than acute anterior infarction. It was encountered in only 7 instances during this study. For this group the conventional tracings were positive in every case, i. e., the take-off was low in lead I and high in lead III. In no instance was information obtained from the precordial tracings which was not in evidence in the first three leads. In fact, in 3 of these cases there was no change in the precordial tracings other than a deep Q wave. This finding was encountered frequently in our study of persons with normal hearts.<sup>1</sup> In several instances a high take-off of the

ST segment was present in the precordial tracings only with the apical lead, and this change was more transient in the precordial tracings than in the conventional lead III (table 1) We did not find the precordial tracings of any additional value in cases of acute myocardial infarction of the posterior type

#### THE SIGNIFICANCE OF AN UPRIGHT T WAVE AS THE ONLY ABNORMALITY IN THE PRECORDIAL ELECTROCARDIOGRAM

In a previous publication it was shown that the T wave was more frequently upright than inverted in tracings taken from certain positions over the precordium This finding, however, was less frequent with the apical position than with other positions over the precordium We did find an upright T wave rarely when the heart was absolutely normal and frequently when there was a diseased heart without myocardial infarction<sup>1</sup>

In the combined review of cases in this and our previous study<sup>1</sup> an upright T wave in the apical lead as the only abnormality of lead IV was found in 47 instances Two of these patients were healthy young nurses with normal hearts, and 2 were young persons who died of a disease entirely unrelated to the cardiovascular system and whose hearts were normal on postmortem examination Two were elderly patients who died of carcinomatosis and whose hearts were normal post mortem Of the remaining, 8 had hypertension and uremia, 2 of whom showed no infarctions at autopsy, 8 had hypertension with cardiac failure, 2 showing no infarction at autopsy Eight had angina, 4 with and 4 without hypertension, none of the patients being examined post mortem Five had valvular heart disease, and the 1 examined post mortem had no cardiac infarction Four had syphilitic aortitis, 2 of whom showed no infarction at autopsy One had bronchopneumonia without obvious heart disease, and 1 had carcinoma of the left lung and a normal heart (verified at autopsy) There were only 4 patients in this group who had evidence suggestive of coronary thrombosis, none of whom were studied post mortem One of these had syphilitic aortitis, and 2 were in the group previously discussed with absence of the Q wave in every lead except the apical, where the entire complex was downward The remaining patient had several bouts of severe precordial pain without fever or leukocytosis

It follows that an upright T wave as the only abnormality in lead IV was frequently encountered However, in the great majority of instances it was not due to cardiac infarction In fact, during this study we did not encounter a single case in which there was indisputable clinical evidence of coronary thrombosis or in which cardiac infarction was present post mortem in which an upright T wave in the precordial lead was the only abnormality

## COMMENT

The recent introduction of precordial leads in clinical electrocardiography has opened up a new method of cardiac diagnosis. So far its practical application has been essentially confined to the diagnosis of myocardial infarction. When electrocardiographic studies were limited to the three conventional leads the technic was simple and standard, so that all data were readily comparable. Now one is faced with a method which gives results that vary greatly, depending on which point over the precordium is explored. The obvious aim is to derive all the useful information in as simple a manner as possible.

This study was undertaken to determine which single point over the precordium affords the most trustworthy information and to discover how often that single point will prove inadequate. We have presented data to show that a tracing obtained with the exploring electrode over the apex of the heart and the indifferent electrode on the left leg furnishes more reliable information than does a tracing from any other single point but that occasionally it may fail to disclose important alterations in the electrocardiogram which could be obtained by the study of multiple precordial leads. In general, this confirms the judgment of F. N. Wilson,<sup>4</sup> who stated that "the information obtained from a single precordial lead is likely to prove misleading, but if, to save time, one lead is taken it is probably best to place the exploring electrode upon the apex beat or in its immediate neighborhood." Just as he has mentioned, we have found a few instances in which absence of the Q wave from a tracing taken with the electrode near the sternum afforded positive evidence of myocardial infarction when the tracings obtained from the apical region did not. It is hoped that with further studies, such as those of Kossman and de la Chapelle,<sup>5</sup> on the part of various investigators general rules will be established regarding the indications furnished by the use of multiple leads, so that for routine practice only the apical position will be necessary but that under specific circumstances other leads will need to be used.

## SUMMARY

For 82 patients who had typical histories and clinical findings of myocardial infarction an electrocardiographic study was made using three conventional leads and nine additional chest leads from over the

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4 Wilson, F. N., in Levy, R. L. *Diseases of the Coronary Arteries and Cardiac Pain*, New York, The Macmillan Company, 1936, p. 281.

5 Kossman, C. E., and de la Chapelle, C. E. *The Precordial Electrocardiogram in Myocardial Infarction. Observations on Cases with Infarction Principally of the Anterior Wall of the Left Ventricle and the Adjacent Septum*, *Am Heart J* 15: 700, 1938.

precordium The main purpose was to ascertain which single point affords the most reliable diagnostic data

Absence of a Q wave<sup>2</sup> from the precordial curves obtained from the apex was the most constant and reliable indication of anterior myocardial infarction In a few instances, several days to four weeks elapsed after the acute attack before the Q wave disappeared In 1 case of anterior infarction a normal Q wave persisted indefinitely When the Q wave did disappear from the apical lead, it was not found to return on follow-up study

The direction of the T wave, though generally upright, was not found to have reliable diagnostic value

A significant deviation of the ST segment from the isoelectric line in the precordial leads occasionally established the diagnosis during the early days following the attack when the conventional leads were not distinctive In these cases there was also associated absence of the Q wave from the apical lead

Precordial electrocardiograms were of no additional value in the diagnosis of posterior infarction

For routine work the precordial lead obtained at the apex was found to be of more value than a lead from any other point over the precordium, and with rare exceptions it disclosed as much diagnostic information as multiple precordial leads

Further investigation is required in the interpretation and application of multiple chest leads in the occasional instances in which the apical lead does not establish the diagnosis

# EFFECT OF BENZEDRINE SULFATE ON GASTRIC EMPTYING AND INTESTINAL ACTIVITY

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In 1937 the Council on Pharmacy and Chemistry of the American Medical Association published a concise review of the literature pertaining to benzedrine<sup>1</sup>. Since the drug is well known, a general discussion of its characteristics is not necessary here.

In a recent paper<sup>2</sup> we reported that in dogs benzedrine given orally decreased the initial emptying time of the stomach to 31 per cent of the normal, but increased the period for final emptying on the average about 14 per cent. Van Liere and Sleeth<sup>3</sup> observed in 3 human subjects the delay in final emptying. More recently Rosenberg, Arens, Marcus and Necheles<sup>4</sup> have confirmed both these observations as to the increased time for final emptying in man and dogs. Investigations conducted on man similar to those previously reported by us led to animal experimentation for an interpretation of these results. We present here our observations concerning the influence of benzedrine on the initial and final gastric emptying in man and evidence from animal experimentation on the manner in which this effect is produced. The action on the stomach, the pylorus and the intact and isolated intestine has been studied.

## METHODS

For the work on man 10 medical students were selected and divided into three groups. To avoid the possibility of cumulative effects of the roentgen ray no

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1 Present Status of Benzedrine Sulfate, report of the Council on Pharmacy and Chemistry, J A M A **109** 2164 (Dec 18) 1937.

2 Beyer, K H, and Meek, W J. Effect of Benzedrine Sulfate on Stomach Activity and Emptying Time, Proc Soc Exper Biol & Med **37** 74 (Oct) 1937.

3 Van Liere, E J, and Sleeth, C K. The Effect of Benzedrine Sulfate on the Emptying Time of the Human Stomach, J Pharmacol & Exper Therap **62** 111 (Jan) 1938.

4 Rosenberg, D H, Arens, R A, Marcus, P, and Necheles, H. Benzedrine Sulfate. Its Limitations in the Treatment of Spastic Colon and a Pharmacologic Study of Its Effects on the Gastrointestinal Tract, J A M A **110** 1994 (June 11) 1938.

group was used more often than once in three weeks. The subjects, having omitted breakfast on the morning of the experiment, were given three 10 mg tablets of benzedrine sulfate each or identical placebos (controls) orally fifteen minutes before the opaque meal<sup>5</sup>

The meal consisted of 60 Gm of finely ground Shredded Ralston (wheat) biscuits, 125 Gm of barium sulfate and 3 Gm of sugar, thoroughly mixed. Immediately after the administration of the drug, 250 cc of whole milk was added to the mixture, which was then stirred during the fifteen minute interval before the test. The milk was absorbed by the biscuits, and the meal assumed a thick consistency, which was necessary if we were to obtain initial emptying intervals of significant duration.

The time of initial emptying was determined fluoroscopically as the time from the beginning of deglutition until the first appearance of the meal in the duodenum. The time of final emptying was taken as the interval between the first observation and the time when none of the meal was observed in the stomach.

In the animal experiments 7 trained dogs having Thiry or Thiry-Vella fistulas of the small intestine were used for the studies of the stomach and intestine. Each of 4 dogs had one Thiry or Thiry-Vella fistula. The other 3 had two Thiry fistulas each. In these 3 animals one of the two fistulas had its extrinsic nerve supply intact, while the other was denervated by sectioning the mesentery and stripping the blood vessels to the segment.

Gastric responses were measured by the balloon-water manometer-tambour method. Air conduction was used and an intragastric pressure of from 120 to 130 mm of water established. The elasticity of the balloon was never a pressure factor.

The activity of the intact intestine was generally recorded by the balloon-mercury manometer method, water conduction being used. Pressures of from 6 to 10 mm of mercury were used. In a few instances air conduction and the balloon-water manometer-tambour system were employed, the pressure being less than 30 mm of water. This was done because Gruber<sup>6</sup> and others have reported variable results in their intestinal work when using pressures of more than 30 mm of water.

When simultaneous studies of gastric and intestinal response were conducted, 20 to 30 mg of benzedrine sulfate in not over 10 cc of distilled water was admitted into the stomach through a second catheter during a normal record. This was followed immediately by 5 cc of distilled water. A normal record is not affected by 15 cc of water administered slowly in this manner. In more drastic attempts to demonstrate an effect of benzedrine on the intact intestine a dose of from 5 mg (total) to 5 mg per kilogram of body weight was given intravenously. Subcutaneous injections and infusions into the fistulas were also tried.

Intestinal segments from 8 pups and 6 rabbits were used. Strips of jejunum and ileum were kept in an open dish of cool Locke's solution. All records were taken from strips less than ten hours old. Segments of from 2 to 3 cm in length were suspended by the Magnus method in Locke's solution oxygenated at 37 C.

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<sup>5</sup> Benzedrine sulfate and placebos were supplied by the Smith, Kline and French Laboratories, Philadelphia.

<sup>6</sup> Gruber, C. M. The Action of Epinephrine, Tyramine and Ephedrine on the Small Intestine of the Unanesthetized Dog, Before and Following the Administration of Cocaine, *J. Pharmacol. & Exper. Therap.* **57**: 347 (Aug.) 1936.



Pyloric activity was recorded by means of a single balloon type pylorograph similar to those described by Wheelon and Thomas<sup>7</sup> Thirteen fasting dogs were used in these experiments

Anesthesia was induced by pentobarbital sodium (30 mg per kilogram, administered intravenously) for the operations on one group of dogs These were kept in upper third stage anesthesia during the experiment by means of injections of 30 to 60 mg of pentobarbital sodium every two to three hours as indicated The other dogs were decerebrated by the method of Sollmann<sup>8</sup> This operation, including placement of the pylorograph, was carried out during preliminary anesthesia induced by ether, which lasted about thirty minutes

To place the pylorograph in position, the abdomen was opened and the duodenum partially sectioned just distal to the pancreas The pylorograph was then carefully passed up through the duodenum and into the pylorus, one flange of the apparatus being placed on either side of the sphincter The semirigid pylorograph was loosely anchored at the site of insertion into the duodenum The duodenal opening was in turn sutured into the abdominal incision in a manner permitting drainage to the exterior The abdomen was then closed except for the duodenal opening The pylorograph was finally connected through a water manometer to a recording tambour as in the case of the apparatus used for gastric studies

Records were not taken until three hours or more after the operation, although the pylorus generally manifested rhythmic activity immediately after the pylorograph was connected to the manometer and pressure adjusted in the system The purpose of this delay was to give the animals time to recover from the immediate effects of the procedure, to allow for adjustment of pyloric tonus and, in the case of decerebrate dogs, to blow off ether

Intrapyloric pressures of from 3 to 10 cm of water were used The position of the pylorograph was checked at the end of an experiment Both respiration and blood pressure were recorded

## RESULTS

*Experiments on Man*—The table represents the data on this portion of the work The average initial emptying time was decreased from 4.8 to 2 minutes, a decrease of 58.3 per cent In other words, benzedrine reduced the interval of 41.7 per cent of the observed normal The standard deviations of the results with different subjects and at different times with a single subject were approximately the same, that for the normal subjects being  $\pm 1.1$  minute and that for a subject after administration of benzedrine  $\pm 0.4$  minute

The average final emptying time was increased 21 per cent by the drug The greatest individual increase in final emptying was 39 per cent In 2 cases there was no significant difference between the emptying time in the corresponding control experiment and that following administration of the drug The normal variations for a single subject exhibited

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7 Wheelon, H., and Thomas, J. C. (a) Observations on the Motility of the Antrum and the Relation of Rhythmic Activity of the Pyloric Sphincter to That of the Antrum, *J. Lab. & Clin. Med.* 6:124 (Dec.) 1920, (b) Observations on the Motility of the Duodenum and the Relation of Duodenal Activity to That of the Pars-Pylorica, *Am. J. Physiol.* 59:72 (Feb.) 1922

8 Sollmann, T. A Method of Bloodless Decerebration, *J. Pharmacol. & Exper. Therap.* 23:153 (March) 1924

a mean value of 16 minutes, with a standard deviation of  $\pm 14$  minutes. The mean variation for a single subject after administration of benzedrine was 30 minutes, and the standard deviation was  $\pm 19$  minutes. This variation seemed to be independent of body weight for the men. Each of the two young women exhibited an increase in the time for final emptying greater than the combined average for the whole group. While the delay in final emptying after benzedrine is definite, it is not as great as the 57 to 436 per cent reported as due to atropine<sup>9</sup> or the 72.8 to 118 per cent delay following administration of ephedrine<sup>10</sup>.

*Animal Experimentation*—Stomach. Benzedrine sulfate given orally in solution had a twofold action on the dog's stomach, as shown in figure 1. The initial response usually occurred within about 8 minutes after the drug was given. This was one of increased rate, increased

*Effect of Benzedrine Sulfate (30 Mg, Given Orally) on the Initial and the Final Period of Gastric Emptying in Man*

Subject	Initial Emptying				Final Emptying					
	Controls		Effect of Benzedrine		Controls			Effect of Benzedrine		
	No of Trials	Average Time, Min	No of Trials	Average Time, Min	No of Trials	Average Time		No of Trials	Average Time	
						Hr	Min		Hr	Min
L E F	2	55	1	25	2	4	52	2	5	56
W B O	2	65	2	20	2	3	34	2	4	04
E L K	2	65	1	20	2	4	05	1	4	17
S P H	2	35	2	25	2	3	23	2	4	03
G G O	2	30	2	20	2	4	23	2	6	06
E W*	2	45	2	15	2	5	11	2	6	32
N A F	2	50	2	20	2	4	35	2	4	27
E S*	2	40	2	20	2	3	40	2	5	22
J H A	2	50	2	20	2	3	32	2	4	33
M J O	2	40	2	15	2	3	45	2	3	47
Total	20		18		20			19		
Average		48		20		4	05		4	57

\* Female

tonus and often increased amplitude of contraction. The effect of increased rate and tonus was to elevate the mean intragastric pressure during this period. However, an inhibitory secondary effect followed within forty minutes after administration of the drug, from which the stomach did not generally recover completely for over an hour. During this secondary phase there was marked inhibition, even to cessation of activity, tonus returning to or falling below its state previous to the influence of the drug.

*Intestine*. We have not been able to demonstrate consistently any influence of the drug on the intestine in situ even in toxic doses (5 mg

<sup>9</sup> Herrin, R. C. The Effect of Atropine and Pilocarpine on the Emptying Time of the Human Stomach, *Am J Physiol* **115** 104 (March) 1936.

<sup>10</sup> Van Liere, E. J., Lough, D. H., and Sleeth, E. K. The Effect of Ephedrine on the Emptying Time of the Human Stomach, *J A M A* **106** 535 (Feb 15) 1936.

per kilogram, administered intravenously) Figure 1 illustrates the refractoriness of a normal Thiry-Vella fistula to the agent

In figure 2 is seen the response to the drug of the isolated intestine from the dog and rabbit Benzedrine regularly increased amplitude of

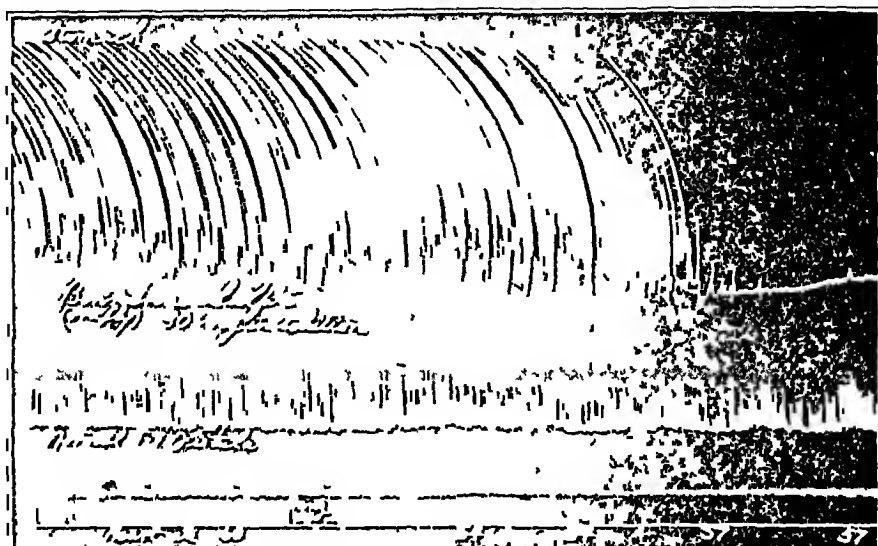


Fig 1—Effect of benzedrine sulfate, 30 mg administered orally, on the activity of the stomach (above) and of a normal Thiry-Vella fistula (below) The heart rate is noted below the base line The time is indicated in five second and one minute intervals

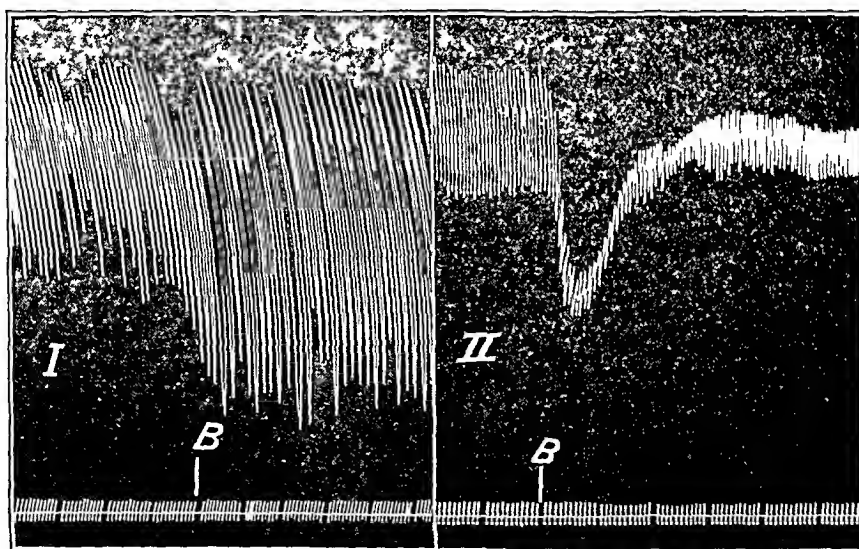


Fig 2—Effect of benzedrine sulfate (in a concentration of 1:12,500) on isolated intestinal strips from the dog (I) and the rabbit (II) Segments were suspended in Locke's solution oxygenated at 37 C Time is indicated in five second and one minute intervals

contraction and decreased tonus and rate of rhythmic activity of segments from the dog. It decreased the amplitude and, slightly, the rate of rhythmicity of intestinal strips from the rabbit. Decrease in tonus, in about half of twenty strips, was usually preceded by a marked initial drop. In the other half tonus was either not affected or only slightly increased. Effective concentrations were found to be 1/8,000 to 1/35,000, 1/12,500 usually being used. Detrick and his co-workers<sup>11</sup> found that in dilutions of 1/500,000 to 1/100,000 benzedrine caused inhibition of segments from the duodenum, ileum and colon of cats but that these concentrations had no effect on tissues from the rabbit, rat or guinea pig. Differing somewhat with these results, Boyd<sup>12</sup> reported that concentrations of from 1/10,000 to 1/100,000 predominantly caused a prolonged spastic type of contraction of the virgin guinea pig uterus and of intestinal strips from the rabbit.

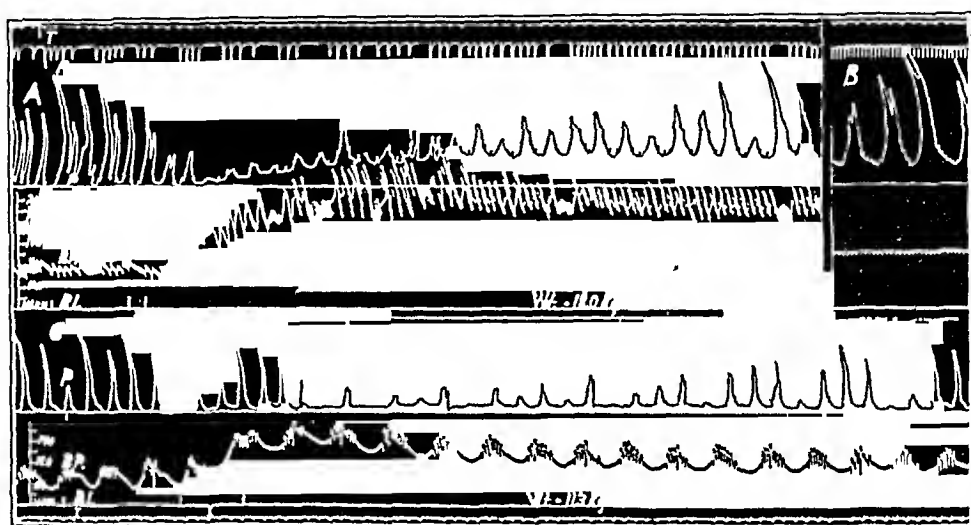


Fig 3—Effect of initial intravenous injections of benzedrine sulfate on the pylorus, blood pressure and respiration. *A*, 0.44 mg per kilogram, rate of injection 378 mg per kilogram per minute, *C*, 0.178 mg per kilogram, rate of injection 0.378 mg per kilogram per minute. *A* and *B* are from a dog under anesthesia induced by pentobarbital sodium, *B* being taken thirty minutes after the injection shown by *A*. *C* is from a decerebrate dog. *R* represents respiration, *T*, time in one minute and five second intervals, *P*, pyloric activity, *BP*, blood pressure in mm of mercury, *BL*, base line for the blood pressure, and *I*, the duration of the injection.

**Pylorus** Since the results for the dogs under anesthesia induced by pentobarbital sodium and those for the decerebrated animals were

<sup>11</sup> Detrick, L. E., Millikan, R., Modern, F. S., and Thienes, C. H. On the Pharmacology of Phenylisopropylamine (Benzedrine), *J. Pharmacol. & Exper. Therap.* **60**: 56 (May) 1937.

<sup>12</sup> Boyd, E. M. The Effect of Benzedrine Sulphate on the Bowel and Uterus, *Am. J. M. Sc.* **195**: 445 (April) 1938.

qualitatively the same, they may be considered together. Benzedrine increased the tonus and inhibited the amplitude of contraction of the rhythmic pylorus (fig 3). Amplitude of contraction was affected by smaller doses of the drug than was tonus. The duration of action was dependent on the concentration of the drug, however, a normal or even increased amplitude preceded the return of normal tonus. In animals anesthetized with pentobarbital sodium the pylorus was not usually affected unless the concentration of the agent was sufficient to cause on the average a 49 per cent rise in blood pressure (approximately 0.23 mg per kilogram at an initial intravenous injection of 15 seconds' duration). However, pressor increases of 31 per cent were sometimes accompanied by a slight decrease in amplitude. We do not mean to imply that blood pressure was a factor in causing the pyloric response, but to point out on a pressor basis the relative insensitiveness of the pylorus to the drug.

**Blood Pressure and Respiration.** A complete analysis of data on blood pressure and respiration does not belong in this paper. Briefly, at the height of the pressor effect vagal beats generally occurred, especially after initial injections, and in 1 instance ventricular rhythm was prolonged. The respiratory rate was always increased by benzedrine under these conditions.

#### COMMENT

Normal gastric emptying is now generally believed to be dependent on the relation between intragastric pressure and resistance at the pyloric sphincter and possibly the duodenal bulb. Many factors are known to modify this pressure-resistance relation. The tandem balloon studies of Wheelon and Thomas<sup>7</sup> and Meschan and Quigley,<sup>13</sup> analyzing the part played by these various factors, have been of particular interest.

In terms of this relation, rate of evacuation may be increased by (1) increased intragastric pressure, (2) decreased resistance at the pylorus and upper part of the duodenum, (3) a combination of these two conditions or (4) disproportion increase or decrease of intragastric pressure and pyloric resistance so that the gastric influence remains dominant. Decrease in the rate of emptying may be explained similarly by reversing the conditions. Thus the rate of emptying is dependent on the combined influences of the factors involved. The increase in initial rate due to benzedrine may be explained by the fourth condition just listed, the increased pyloric resistance not being sufficient to overcome the increased intragastric pressure due to the drug. The delay in final emptying is obviously due to the gastric inhibition.

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<sup>13</sup> Meschan, I, and Quigley, J. P. Spontaneous Motility of the Pyloric Sphincter and Adjacent Regions of the Gut in the Unanesthetized Dog, *Am J Physiol* **121** 350 (Feb.) 1938.

Myerson and Ritvo,<sup>14</sup> from fluoroscopic and roentgenographic evidence, suggested that the stomach empties more rapidly under the influence of benzedrine because peristaltic activity of the stomach is only slightly decreased and the sphincter is relaxed. From these observations, they recommended benzedrine for the relief of pylorospasms, facilitating roentgenoscopy of adjacent regions. Since gastric emptying is the result of several factors of resistance and pressure, it is doubtful if tonicity of the pylorus or stomach can be accurately deduced from fluoroscopic determinations.

We have found that gastric activity and intragastric pressure are increased at first after ingestion of benzedrine. Our experiments indicate that benzedrine would, if anything, tend to increase tonicity and inhibition of pyloric rhythmicity rather than relieve it. However, the marked increase in initial rate of evacuation reported by us here and previously suggests that the increased tonicity of the pylorus is not sufficient to overcome the effect of the initial gastric stimulation by the drug.

#### SUMMARY

In man benzedrine sulfate was found to decrease the time for initial emptying of the stomach to about 42 per cent of the observed normal and to increase the average time for final emptying 21 per cent.

The decrease in initial emptying time of the normal stomach following administration of benzedrine is probably due to the primary increase in tonus and activity of the stomach raising intragastric pressure and forcing the contents through a pylorus the tonus of which, if altered by the drug, may relatively be only slightly increased, rhythmicity being correspondingly diminished. The delay in final emptying is due to secondary inhibition of the stomach and possibly increased pyloric tonus. While the stomach does not fully recover from the secondary inhibition for over an hour, final emptying is not prolonged to a very significant extent.

Only by using excised intestinal strips and concentrations unapproachable in the normal animal could we demonstrate any effect of the drug on the intestine.

These results suggest that what value benzedrine has in overcoming functional pylorospasm of a moderate degree is probably due to initial gastric stimulation overcoming pyloric resistance rather than to any direct inhibiting effect on pyloric tonus.

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14 Myerson, A, and Ritvo, M. Benzedrine Sulfate and Its Value in Spasm of the Gastro-Intestinal Tract, *J A M A* **109** 23 (July 4) 1936. Ritvo, M. Drugs as an Aid in Roentgen Examination of the Gastro-Intestinal Tract. The Use of Mecholyl, Physostigmine, and Benzedrine in Overcoming Atonicity, Sluggishness of Peristalsis, and Spasm, *Am J Roentgenol* **36** 868 (Dec.) 1936.

# NEPHROSIS DUE TO CARBON TETRACHLORIDE

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The number of clinical reports of cases of carbon tetrachloride poisoning with renal symptoms comparable to those of acute nephritis or toxic nephrosis is steadily increasing. Although symptoms referable to hepatic damage are usually present in such cases, they are soon overshadowed by signs indicating severe renal damage. The intoxication is due either to inhalation in a poorly ventilated room of fumes of carbon tetrachloride used for cleaning purposes or in fire extinguishers or to ingestion of this chemical.

The clinical symptoms and laboratory findings observed in such cases are so characteristic and uniform that the correct diagnosis can be made without an adequate clinical history of carbon tetrachloride poisoning. Indeed, the clinical picture sometimes prompts specific inquiries pertaining to the use of this chemical. The patients suffer from headache, dizziness, general malaise, fever and sometimes irritation of the nasal and conjunctival mucous membranes. Soon there appear signs of gastric irritation characterized by nausea, vomiting, diarrhea and not infrequently hematemesis, jaundice sets in and may attain a considerable degree of severity. After several days, during which the gastrointestinal symptoms remain more or less stationary and the jaundice increases, there appear clinical signs of renal involvement, such as oliguria, progressing sometimes to anuria, epileptiform convulsions, hypertension and generalized edema, cyanosis and pulmonary edema may develop, and uremic coma is not rare. Commonly a hemorrhagic diathesis is observed. Not all these symptoms may be present, but most of them are observed in the majority of cases.

## LABORATORY FINDINGS

The nonprotein nitrogen content of the blood is elevated, with reported values up to over 200 mg per hundred cubic centimeters, the urea content, up to about 200 mg, the uric acid content, up to 12 mg, the creatinine content up to 10 mg, and the inorganic phosphorus content up to 11 mg. The values for sugar vary from 125 to 155 mg per hundred cubic centimeters. The chloride value is around 500 mg, the calcium value between 9 and 10 mg and the cholesterol value about 140

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mg Sometimes the reported values for phospholipids are low, and the ratio of ester cholesterol to total cholesterol is diminished. Some authors report a lower levulose tolerance and a reduced fibrinogen content. The guanidine level is elevated. The value for protein is within normal limits, the carbon dioxide-combining power is lowered, varying between 25 and 42 volumes per cent. The icteric index varies between 12 and 30 in different cases. In the early stage there may be polycythemia, which is sometimes followed by anemia, depending on the degree of hepatic damage. There is leukocytosis, the count ranging from about 10,000 to 35,000 per cubic millimeter, with polymorphonuclears predominant.

The blood pressure is markedly increased, and values from 200 to 300 mm of mercury, with a high diastolic pressure, are not unusual.

The urine is scanty and contains albumin, often there are red blood cells, white blood cells and casts.

Most of the patients reported on in the literature recovered even after having been in uremic coma. Recovery is rapid and complete, but leukocytosis may persist and the renal function may be below normal for some time. The improvement is accompanied by the return to normal values for nitrogenous waste products in the blood and by the return of the icteric index to normal, the urine increases in amount and becomes free from albumin, red blood cells, white blood cells, bile and casts.

#### REPORT OF CASES

Within the last year 3 patients with carbon tetrachloride poisoning have been observed in the Presbyterian Hospital. Two of the patients died, and autopsies were performed, 1 patient recovered. Dr W W Palmer has given me permission to publish the following case histories from the records of the hospital.

**CASE 1**—A 71 year old white man, a photographer, was admitted to the hospital on March 21, 1937, because of painless jaundice following intake of some fluid containing carbon tetrachloride eight days previously (the exact amount of carbon tetrachloride ingested could not be ascertained).

**Past History**—He had always been in good health and active. There was, however, a history of chronic alcoholism.

**Present Illness**—There were no immediate effects after the chemical was swallowed, nausea and vomiting began the following night and continued for eight days, until admission to the hospital. Jaundice appeared on the second day and anuria on the sixth day. There had been no bowel movement during the past eight days. There had been complete anorexia during this period. The patient was semistuporous on entry.

**Physical Examination**—The temperature was 97.4 F, the pulse rate 80 and the respiratory rate 22. The blood pressure was 140 systolic and 85 diastolic. The patient complained of constant nausea and was intensely jaundiced. The head and chest were essentially normal except for pulmonary emphysema. The abdomen



was distended, with the skin drawn tight, there were shifting dulness and a definite fluid wave. The bladder was distended. The edge of the liver was at the costal margin. No tenderness or mass was noted.

*Laboratory Findings*—Examination of the blood showed hemoglobin, 120 per cent, red blood cells, 5,600,000 (the cells were normal as to size and shape but showed some variation in the hemoglobin content), white blood cells, 13,680, polymorphonuclears, 91 per cent, lymphocytes, 7 per cent, and mononuclears, 2 per cent. There was a normal number of platelets. Chemical analysis of the serum showed inorganic phosphorus, 6.5 to 7.8 mg per hundred cubic centimeters, bilirubin, 13.6 to 14 mg, chlorides (as sodium chloride) 500 mg, calcium, 8.7 mg, sugar, 126 mg, nonprotein nitrogen, 165 mg, phosphatase, 63 Bodansky units, carbon dioxide, 44 volumes per cent, total protein, 7.2 Gm, albumin, 3.7 Gm, globulin, 3.5 Gm, and euglobulin, 1.1 Gm. Urinalysis showed specific gravity of 1.015. There were a 3 plus reaction for albumin, a 0 to 1 plus reaction for acetone and a 2 plus reaction for bile. There was no sugar. There were a few red blood cells, white blood cells and cellular casts. The urine was straw colored. The stools were soft and light yellow. There were no gross blood, mucus, parasites or ova. There was a 1 plus reaction for bile. The guaiac test gave a negative reaction.

*Course*—The patient was given fluid containing dextrose parenterally, but in spite of large infusions the urinary output remained small. On the tenth day of illness he was found gasping for breath. He was cyanotic and had prolonged expirations. The lungs were clear, the pulse rate was slow and regular. He became progressively more cyanotic and stopped breathing ten days after taking the carbon tetrachloride. The final clinical diagnosis was carbon tetrachloride poisoning, acute yellow atrophy of the liver with cholemia, nephrosis and pulmonary emphysema.

*Autopsy Data*—Examination was performed three hours after death.

*Gross Examination* The skin was intensely and uniformly icteric. The thorax was barrel shaped. There were no other relevant external findings.

The peritoneal cavity contained 2,000 cc of clear yellow fluid. The peritoneal surfaces were smooth and glistening, the organs were normally disposed and the edge of the liver was at the costal margin. The pleural cavities and pericardial sac were normal. The heart, spleen, pancreas and adrenal glands were normal. The aorta was arteriosclerotic, and the lungs were emphysematous. The liver weighed 1,220 Gm, it was definitely smaller than normal and soft. The surface was finely granular, the parenchyma was intensely jaundiced and the central zones were sunken and dark reddish brown. There was a slight increase in the amount of fibrous tissue about the portal canals. Numerous tiny yellowish flecks were seen in the midportion of the lobules. No gross changes were apparent in the biliary passages or vessels. The gallbladder was normal. The kidneys weighed 160 Gm (right) and 200 Gm (left), respectively. When the capsule was incised, the renal tissue bulged through, suggesting swelling of the parenchyma. The kidneys were of similar appearance. The capsules stripped easily, leaving a surface which was in places slightly irregular. The parenchyma was a dull reddish brown, through which a greenish tint was observed. On section the kidneys appeared swollen. The cortex was wide, pale and firm, and its striations were blurred, while those of the pyramids were distinct. The centers of several of the pyramids showed yellow streaks parallel to the striations. There were numerous indistinct yellowish areas throughout the cortex. The blood vessels were not unusual. A double pelvis was found on the right side, with the ureters

uniting to form a common ureter 3 cm below the calices. The mucosa of the pelves and ureters was normal. The bladder was small and contracted and the mucosa greenish yellow. There were ecchymoses in the posterior wall. The prostate was enlarged, otherwise it was not remarkable. The testes, epididymides and seminal vesicles were normal. The esophagus was normal. The mucosa of the stomach was covered with a thick layer of mucus, the mucosa underneath appeared normal. The small and large intestines were grossly normal. The brain and spinal cord were not removed.

Chemical analyses of the hepatic and renal tissue for mercury, arsenic and lead showed no excessive amounts.

**Microscopic Examination** The liver showed extensive central necrosis, degeneration of the cells and early regeneration in the periphery of the lobule. There

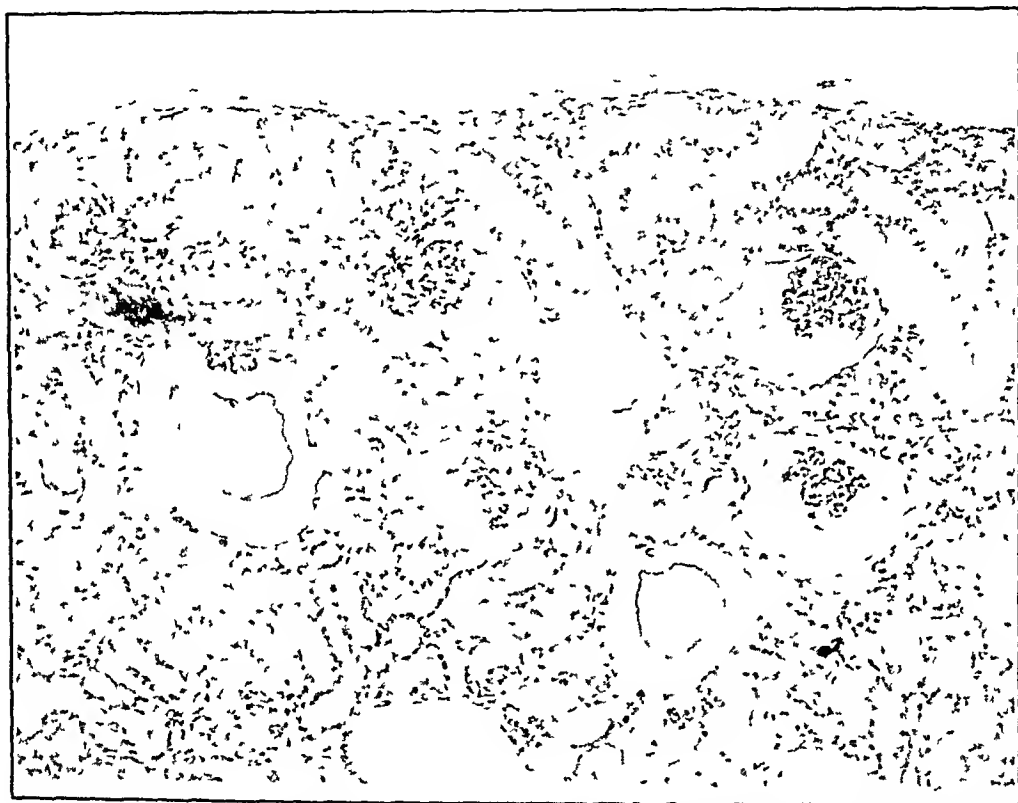


Fig 1—Cross section of the kidney, showing distention of the glomerular spaces with albuminous material, and casts and granular precipitate in the lumens of the tubules,  $\times 60$

were hemorrhages in the central areas. No evidence of proliferation of the bile ducts was seen. Bile plugs were present in some of the canaliculi. In the kidneys the glomeruli were somewhat larger than normal, and the capillary loops were congested. The tufts were rather poor as to cells. The space of Bowman was greatly distended with pink-staining granular precipitate, which sometimes was compressing the tufts. The epithelial cells lining the spaces were sometimes swollen, projecting into the lumens. The basement membrane of the glomeruli appeared swollen and irregularly thickened (fig 1). The epithelial cells of the proximal convoluted tubules were swollen, granular or vacuolar, and the lumens contained granular precipitate or hyaline casts, which sometimes were bile stained. The lumens of Henle's loops and those of the distal convoluted

tubules were greatly distended with hyaline and cellular casts, which sometimes were bile stained. The lining cells of these tubules were irregular as to size and were frequently sloughed off as single cells or in toto, not infrequently a new lining had been formed, so that the casts were surrounded by a double layer of epithelial cells, most of which showed signs of degeneration. A rare mitotic figure could be seen in the lining cells. Many of the collecting tubules contained hyaline or cellular casts. In addition to the casts, bodies of various sizes were free within the lumens of the convoluted tubules and those of Henle's loops, they were either pale yellowish green or more or less deeply stained with hematoxylin. These concretions showed a definite radial arrangement and were brilliantly doubly refractive. There was edema of the cortex and moderate congestion of the pyramids. Stains showed a small number of fine fat droplets in the lining cells of Henle's tubules. With von Kossa's stain the concretions became black. The other organs showed no relevant pathologic changes.

*Anatomic Diagnosis*—The diagnosis was poisoning due to carbon tetrachloride, central necrosis of the liver, jaundice, ascites, nephrosis due to carbon tetrachloride, advanced arteriosclerosis of the aorta, with calcification and ulceration, chronic bronchitis, mild bronchiectasis, pulmonary emphysema, mild hemorrhagic cystitis, and congenital malformation of the right kidney (double pelvis).

**CASE 2**—A 37 year old Negress, a housemaid, was admitted on May 22, 1937, because of vomiting, diarrhea, chills, fever and painful muscle spasms for forty-eight hours.

*Family History*—The family history was irrelevant.

*Past History*—Spontaneous abortion, necessitating a pelvic operation, occurred in 1918. There was a history of chronic alcoholism, frequent excesses being customary.

*Present Illness*—Three days before entry she was cleaning dresses with carbon tetrachloride in a close, stuffy room for three hours. Afterward she drank a glass of cold milk and suddenly had an attack of moderately severe cramplike pain, with a sense of fulness in the epigastrium. Soon she began to vomit and had vomited repeatedly since. Although she was usually constipated, diarrhea developed, with seven to eight movements a day for the past forty-eight hours. On the second day of her illness she began to have severe pain, with spasms of the muscles, and was seen by a physician. She had a carpopedal spasm, and the Chvostek sign was elicited. Calcium lactate and phenobarbital failed to relieve the pain.

*Physical Examination*—The temperature was 103.6 F, the pulse rate 88, the respiratory rate 26 and the blood pressure 100 systolic and 56 diastolic. The patient was poorly developed and thin, she was excited and terrified and was crying. She was breathing rapidly while lying in bed with her arms flexed across her chest and her hands showing carpopedal spasm. The pupils were contracted, irregular and fixed. The conjunctiva was injected, and there was milky opacity of the right lens. No jaundice was evident. The breath smelled of acetone. The teeth were carious. The neck was not stiff, and the thyroid gland was not enlarged. The lungs were clear. The heart was normal, with a rapid rate. The abdomen was tense, there was slight tenderness in the right lower quadrant on depression, without rebound tenderness or spasm. The reflexes were normal. The Chvostek and Trousseau signs were elicited.

*Laboratory Findings*—The laboratory findings are given in table 1. A specimen of the cleaning fluid was examined and was found to be carbon tetrachloride.

*Course*—There was an almost complete shutdown of the function of the kidneys for a period lasting for several days, in spite of the administration of large infusions of Ringer's solution and of 10 per cent solution of dextrose. It was thought that the patient was suffering from the effects of carbon tetrachloride poisoning due to inhalation of vapors while working in a poorly ventilated room. Both the liver and the kidneys were thought to be affected, because there were bile in the serum and urine, almost complete anuria, albumin and blood elements in the urine and marked nitrogen retention. The generalized tetany was thought to be related to cholemia. Forcing of fluids was continued, and after three

TABLE 1—*Laboratory Findings (Case 2)*

	5/22	5/24	5/29	6/2	6/8	6/28
Carbon dioxide content, vol %	54.5	43.3				
Chlorides (as sodium chloride), mg per 100 cc	478	515	602		575	
Inorganic phosphorus, mg per 100 cc	5.6	4.2	4.3	3.9	2.4	
Sodium, mEq per L	124.5	120.0				
Potassium, mEq per L		6.1				
Calcium, mg per 100 cc	9.7	8.1		8.8	9.8	
Total lipids, mg per 100 cc		1,185		684		
Phospholipids, mg per 100 cc		236		190		
Neutral fat, mg per 100 cc		760		270		
Total fat, mg per 100 cc		215		204		
Free cholesterol, mg per 100 cc		77		87		
Combined cholesterol, mg per 100 cc		133		117		
Bilirubin (direct), mg per 100 cc	4.5	4.7	3.5	4.0	2.0	Trace
Phosphatase, Bodansky units per 100 cc	4.7	4.0	4.4	5.0	4.6	
Nonprotein nitrogen, mg per 100 cc	63	82	94	66	37	26
Protein, Gm per 100 cc	7.8	5.9				7.5
Albumin, Gm per 100 cc	4.4	3.3				3.9
Globulin, Gm per 100 cc	3.4	2.6				3.6
Duglobulin, Gm per 100 cc	0.7	0.5				
Sedimentation rate, mm	10				60	62
Hemoglobin, %	85	65	57		70	67
Red blood cells, million per cu mm	4.3	3.6	3.3		3.9	3.4
White blood cells, per cu mm	13,250	6,900	22,700	13,250	6,700	6,900
Polymorphonuclears, %	87	51	82	53	60	51
Lymphocytes, %	5	42	13	33	29	42
Monocytes, %	4	5	3	6	10	5
Eosinophils, %	2	2	1	2	0	0
Basophils, %	2	0	1	1	1	2
Platelets	Normal	Normal	Normal	Normal	Normal	Normal
Blood pressure	100/50	130/78	112/80		100/70	94/64
Urine albumin	++++	+++	+	0	+	0
bile	+	0	0			
red blood cells	+	+	+	0	0	
white blood cells	+	+	+	+	+	0

days of anuria the patient began to pass urine, after the first week the output of urine rose to over 1,000 cc a day. The nonprotein nitrogen reached values close to 100 mg per hundred cubic centimeters at the end of the first ten days, but with continued treatment it began to drop, at the same time the values for blood urea and nitrogen, inorganic phosphorus and bilirubin returned to normal. Eleven days after the onset, fever developed, and she showed signs of consolidation of the lungs, without dyspnea or cough. An electrocardiogram taken at this time suggested myocardial damage. The patient was kept in bed as long as the electrocardiographic changes were present, she had a low grade fever and an elevated sedimentation rate, for which residual hepatic damage was held responsible. She was allowed to go home on June 30 for further rest, forty-six days after the beginning of her illness. She was seen in the clinic on July 19

and seemed much improved. Her only complaints were of slight swelling of the ankles and a capricious appetite.

The final clinical diagnosis was poisoning due to carbon tetrachloride, toxic hepatitis, acute renal tubular damage, toxic myocarditis, lobular pneumonia (organism unknown) and cirrhosis (?) of the liver.

**CASE 3**—A 35 year old Negro, a dry cleaner and interior decorator, was admitted to the hospital on Oct 10, 1937, because of dyspnea and cough, with bloody sputum, of eight days' duration. Most of the following history was supplied after the patient's death by his co-worker and by his physician.

The patient was well until eight days before entry, when he returned from work and noted dyspnea. He had been cleaning furniture and draperies with a cleaning solution containing perchlorethylene and trichlorethylene or carbon tetrachloride. According to the statement of his physician, he had run out of the cleaning fluids which he ordinarily used and had purchased several gallons of carbon tetrachloride in order to finish his work. Several hours after this exposure to the vapors of the chemical, which had lasted for several hours, he became acutely ill, with headache, dizziness and malaise, he was nauseated and vomited repeatedly. His pulse rate at that time was over 100 and his blood pressure about 160 systolic. The physician prescribed sedatives and digitalis, which gave no relief. The next day the patient was still nauseated and was vomiting. Several days after this his physician saw him again and noticed a peculiar dusky discoloration of the skin, the patient still complained of gastrointestinal symptoms. Both his co-worker and his physician stated that he was a steady and heavy drinker. Eight days after the onset of his illness he was sent to the hospital by another physician, with a diagnosis of probable bleeding gastric ulcer or early pulmonary tuberculosis. Just previous to entry he had had some difficulty in voiding, the nature of which was not ascertained.

**Physical Examination**—The temperature was 99.4 F, the pulse rate 130, the respiratory rate 36 and the blood pressure, 220 systolic and 125 diastolic. The patient appeared well developed and well nourished. He was thrashing about in bed, gasping for breath. He coughed frequently, raising bloody, frothy sputum. The skin was moist and warm. The pupils were small (morphine). There were large, symmetric scleral hemorrhages lateral to the corneas. The pharynx was edematous and injected. No local or general glandular enlargement was noted. The trachea was in the midline, and the thyroid gland was normal. The heart was enlarged to the right and to the left. There was marked gallop rhythm, the rate was rapid and a systolic apical murmur was heard. The lungs were normal to percussion, wet râles were present throughout both lungs, front and back. The breath sounds were normal. The liver was enlarged, extending to the umbilicus. There were no other masses. No edema was present in the extremities. The radial pulses were equal, the nail beds were cyanotic. There were symmetric macular ecchymoses on the lateral aspect of the upper portion of both arms.

**Laboratory Findings**—The blood count showed hemoglobin, 97 per cent, red blood cells, 5,750,000 (cells and platelets, normal), white blood cells, 36,000, polymorphonuclears, 95 per cent, and lymphocytes, 5 per cent. The nonprotein nitrogen content was 188 mg per hundred cubic centimeters. The sedimentation rate was 18 mm. The Wassermann test gave a negative reaction.

**Course**—Because of the scleral and dermal ecchymoses, purpura was suspected. Pericardial hemorrhage with tamponade was considered a possibility. However, no definite clinical diagnosis could be made. Phlebotomy (360 cc) was per-

formed, and he was given 8 cc of digalen intramuscularly, he responded to that and became quieter with additional doses of morphine. His lungs appeared to clear somewhat, and he rested quietly. Soon, however, pulmonary edema developed, and he died fifteen hours after entry. The clinical impression was as follows: hypertensive cardiovascular disease with cardiac failure (?) and acute nephritis (?) of unknown type.

*Autopsy Data*—The examination was performed eight hours post mortem.

*Gross Examination* Externally no abnormalities were noted except for the ecchymoses and the slight icterus of the scleras. The body cavities contained no fluid, and the visceral surfaces of the organs were smooth and glistening. There were petechial hemorrhages in all the serous membranes. The heart was normal. The aorta showed early atheromatous changes. The lungs weighed 1,000 Gm each and showed marked edema and early consolidation. The spleen, pancreas and adrenal glands were normal. The liver weighed 1,900 Gm. It was soft, and on cut section the central portion of the lobules was dark red and sunken, while



Fig 2—Gross appearance of the kidney on cross section

the periphery showed an ocher yellow tint. The bile ducts and blood vessels were not remarkable. The gallbladder and common duct were normal. The kidneys weighed 220 Gm each, and their capsules stripped easily (fig 2). There was a large extracapsular hemorrhage in the region of the lower pole of the left kidney, and petechiae and ecchymoses were present on the surfaces of both kidneys. The organs were swollen, and on cut section the cortex was bulging. The consistence was much softer than normal. The cortex measured 1 to 1.3 cm in width, and its radial structure was obscured; it was a pale yellowish brown. The pyramids were pink, and their striations appeared less distinct than normal. The renal pelvis were of normal size and showed many ecchymoses and petechiae. The ureters were normal. The bladder was distended with 500 cc of cloudy urine containing flecks of fibrin; its mucosa was swollen and showed many ecchymoses. The urine contained red blood cells, white blood cells and casts. There were a 3 plus reaction for albumin and a 2 plus reaction for bile. The prostate, testes and seminal vesicles were normal. The mucosa of the stomach was dark red, its folds were prominent and were covered with a layer of mucus. The mucosa

of the small intestine and the appendix appeared normal. The mucosa of the cecum was edematous and showed some ecchymoses. There was a large diffuse hemorrhage into the tissues of the root of the mesentery. The cervical organs were normal. The marrow of the femur was fatty and that of the vertebra grayish red. The brain and spinal cord were not removed. Postmortem culture of blood was sterile. Hepatic and renal tissues were analyzed for arsenic and mercury, and normal values were reported.

**Microscopic Examination** The heart and aorta were normal. The lungs showed early lobular pneumonia, sometimes with the formation of a hyaline membrane. Edema fluid was present in most alveoli of both lungs, and there was slight acute bronchitis. The liver showed marked central necrosis, with secondary distention of the central sinusoids. There were degenerative changes in the hepatic cells in the intermediate zone, without signs of regeneration. Fatty changes were noted in the hepatic cells about the portal canals. Within the central necroses there were many phagocytic cells holding golden yellow pigment granules, which gave a partially positive reaction for iron, there was condensation of reticular fibers in the central areas. The gallbladder and pancreas were normal. The adrenal glands and the spleen were normal. In the kidneys the capillaries of the glomerular tuft were congested, and the capsular spaces contained much granular precipitate, which was sometimes so abundant as to push aside the tuft. The basement membrane of the glomeruli was swollen and prominent. The epithelial cells lining the space of Bowman were swollen and were projecting into the lumen (fig 3A). The epithelial cells of the proximal convoluted tubules were swollen, granular and vacuolated, rarely, hyaline droplets were seen (fig 3B). Many of the distal convoluted tubules showed necrosis of their lining cells, many of which had sloughed off, there was early regeneration, and rare mitotic figures were present in the lining cells (fig 4). Most of the convoluted tubules and those of Henle's loops were distended by granular, sometimes hyaline, eosinophilic material. Many small, round concretions showing a radial arrangement were seen in the lumens of these tubules, some of them took the hematoxylin stain, while others did not and were a pale yellowish green (fig 5A). All bodies showed double refraction under the polarizing microscope (5B). The stroma of the cortex and medulla was edematous, and the capillaries of the medulla were congested, a few small hemorrhages were present. Many of the tubules of the medulla—especially the collecting tubules—were plugged with granular, hyaline or cellular casts. Extensive hemorrhages were present about the renal pelvises, sometimes accompanied by polymorphonuclear leukocytes. Stains for fat showed only a few small droplets in the epithelial cells of the convoluted tubules. Von Kossa stains brought out the concretions in the tubules. The bladder showed hemorrhagic cystitis. The prostate, testes and seminal vesicles were normal. The mucosa of the stomach was congested and showed a few polymorphonuclear infiltrations. The small intestine was normal. There were moderate congestion and edema of the submucosa of the cecum. The thyroid and parathyroid glands were normal. The bone marrow was normal.

**Anatomic Diagnosis**—The diagnosis was poisoning due to carbon tetrachloride, central necrosis of the liver, fatty liver, nephrosis due to carbon tetrachloride, edema of the lungs, early acute bronchitis, bilateral lobular pneumonia, and hemorrhages in the lungs, pleura, pericardium, mesentery, renal pelvises, retroperitoneum, conjunctiva and skin.



Fig 3—4, showing albuminous material in the capsular space and swelling of the epithelial cells lining the space of Bowman,  $\times 230$  B, showing swelling and vacuolation of the epithelial cells of proximal convoluted tubules and edema of the cortical stroma,  $\times 460$



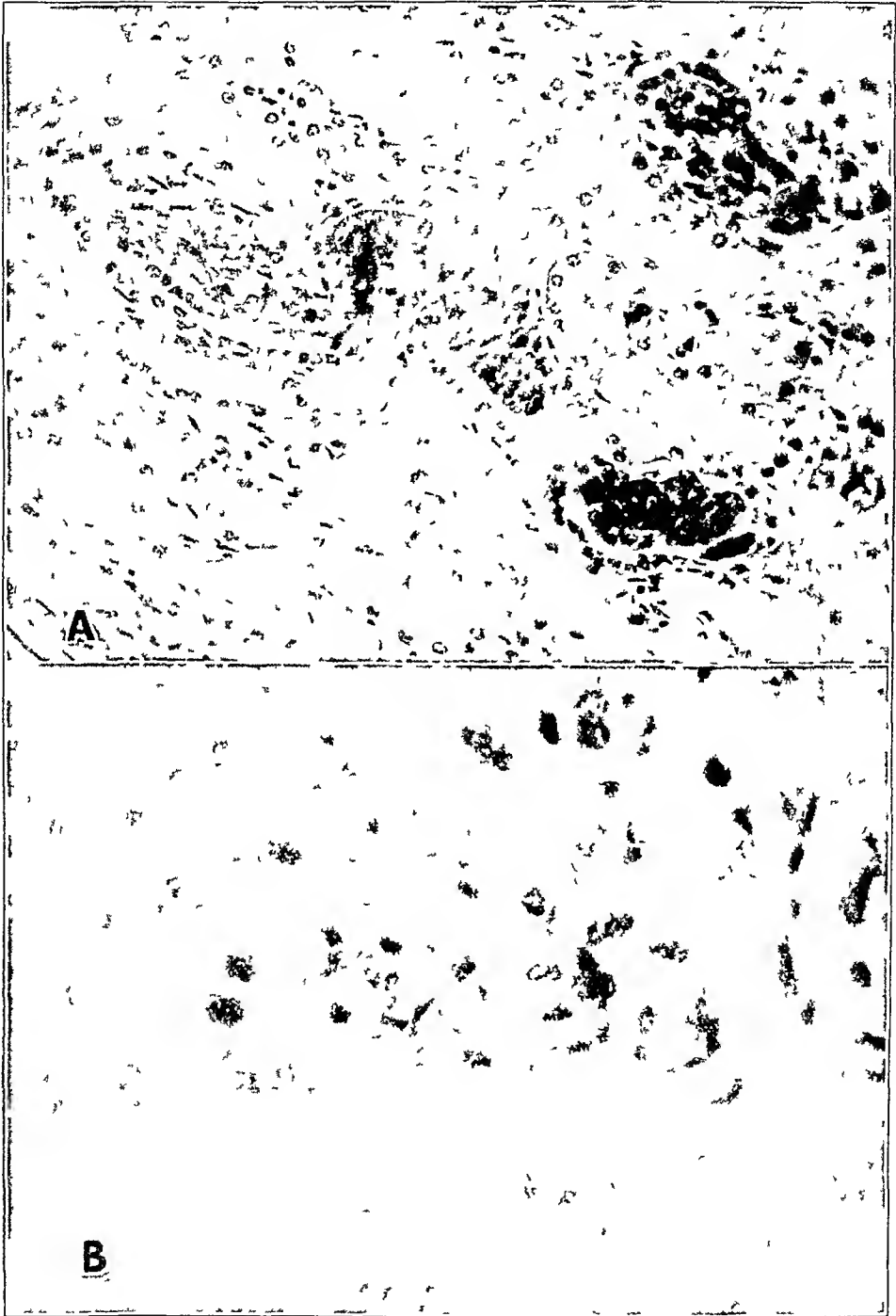


Fig 4—*A*, showing granular and cellular casts in the lumens of distal convoluted tubules,  $\times 230$  *B*, showing granular and cellular cast in the lumen of a distal convoluted tubule, with partial sloughing of the lining cells,  $\times 460$



Fig 5—4, showing a cast and concretions in the lumen of a distal convoluted tubule B, showing double refraction of the concretions under the polarizing microscope,  $\times 460$

## COMMENT

In all 3 cases there was remarkable uniformity of the clinical pictures, conforming with the reports of similar cases in the literature. Likewise the pathologic changes in the 2 fatal cases were essentially alike and corresponded with those described by some observers, particularly by McMahon and Weiss.<sup>7</sup> Aside from the lesions in other organs—especially in the liver—there was clinical evidence of functional damage of the kidneys, recognized by the presence of albumin in the urine, oliguria, nitrogen retention, edema and acute hypertension. The albuminous casts within the glomerular spaces and tubules may be considered as anatomic evidence of functional damage of the glomeruli, anatomic changes in the glomerular tufts were not seen. The necrosis of tubular cells was probably due to a greater concentration of the damaging agent after reabsorption of water within the tubular system and was similar to but not so extensive as that seen in mercury bichloride poisoning. Calcification of the necrotic tubular cells—commonly observed in cases of mercury bichloride poisoning and lasting for ten days or longer—is not a feature in nephrosis due to carbon tetrachloride poisoning, perhaps because of its shorter course in fatal cases. Whether the oliguria was due to mechanical obstruction of the tubules by cellular and albuminous casts or to functional disorder is difficult to say. The nitrogen retention and acute hypertension were similar to those observed in case of mercury bichloride poisoning and were probably of similar origin.

The chemical nature of the globular concretions seen in the tubules of the kidneys in the 2 fatal cases has not been identified, and their significance is not clear. Their refractility under the polarizing microscope disappeared quickly after the addition of a few drops of normal solution of hydrochloric acid and vanished slowly after the addition of normal solution of sodium hydroxide. No change could be observed after the addition of 10 per cent acetic acid or any of the organic solvents, such as alcohol, acetone, benzene or xylene. All the bodies were blackened by the von Kossa stain, indicating that they contained either phosphate or calcium or both. After microincineration the organic framework of the concretions was lost, and only specks of a slightly refractive matter were left, after the addition of normal solution of hydrochloric acid, their refraction disappeared. It must be pointed out that similar bodies were occasionally seen in sections of kidneys which showed no pathologic lesions, a few were also observed in a case of mercury bichloride poisoning. It is perhaps the large number of such concretions that is of some significance, and their presence should be checked in the future in cases of carbon tetrachloride poisoning.

Concerning the modes of carbon tetrachloride poisoning, two major ones can be distinguished, intake by mouth and inhalation of fumes

Absorption through the skin (shampoo, dipping of arms or other methods) should perhaps be considered but this type is probably always complicated by inhalation of the vapors. An analysis of the cases of carbon tetrachloride poisoning reported in the literature indicates a greater percentage of renal symptoms in cases of poisoning due to inhalation, likewise, the anatomic lesions in the kidneys seem more common in the fatal cases of this type. Data are given in table 2 with regard to all the cases reported in the literature and the 3 present cases. According to Lamson and his associates,<sup>38</sup> the concentration of carbon tetrachloride is greater in the portal circulation than in the general circulation after ingestion of the chemical, in cases of poisoning due to inhalation, the concentrations of carbon tetrachloride reaching the liver and the kidneys are about equal. This may perhaps explain the greater susceptibility of the kidneys in cases of carbon tetrachloride poisoning by inhalation.

While the influence of alcoholism cannot be correctly evaluated because many of the reports omit reference to this point, it seems definite

TABLE 2—Cases of Acute Carbon Tetrachloride Poisoning Reported in the Literature

	By Mouth	Inhalation of Fumes	Total
Numbers of cases	32	99	131
Clinical symptoms of renal damage	6	27	33
History of alcoholism	4	9	13
Fatal cases	21	18	39
Autopsy reports	19	6	25
Anatomic evidence of renal damage	12	7	17

that it played a role in some of the cases. In this connection case 3 is interesting because the co-worker of the patient, a teetotaler, had been working in the same room and had been exposed to the vapors of carbon tetrachloride for the same length of time. Although he felt the effect of the exposure and suffered from headache and gastrointestinal distress, he recovered quickly after breathing fresh air. The role of alcoholism in carbon tetrachloride poisoning has been pointed out repeatedly and has been discussed by Lamson, Minot and Robbins.<sup>6</sup> According to their view, alcohol either effects a greater absorption from the gastrointestinal tract or causes greater penetration into the liver. The mechanism of its influence in carbon tetrachloride poisoning by inhalation is obscure, but its effect cannot be denied. The reduction of the glycogen store in the hepatic cells of alcoholic addicts may have some importance in the greater susceptibility to carbon tetrachloride poisoning. On the other hand, there have been many instances in which carbon tetrachloride poisoning did not depend on alcoholism.

The transient mild polycythemia which has repeatedly been observed<sup>40</sup> and which was present in all 3 cases presented here is probably due to

the hemoconcentration after repeated vomiting, in cases of prolonged involvement it may be followed by anemia, depending on the degree of damage to the liver

The fall in the fibrinogen content of the blood observed in cases of carbon tetrachloride poisoning<sup>41</sup> explains the hemorrhagic diathesis, which is a common clinical symptom and which was observed in case 3. According to Lamson, Minot and Robbins,<sup>39</sup> hemorrhages may be uncontrollable when both the calcium ion and the fibrinogen content of the blood are low. In this respect cholemia is of importance because of the precipitation of calcium by bile. If the calcium reserve is low, tetany, tremors and convulsions may occur. In case 2 such a picture was presented.

The plasma lipid content was determined only in case 2 (table 1). During the acute phase of the disease the total lipid content was found to be high, owing to the increase in neutral fats, while the values for phospholipids and cholesterol were within normal limits. The presence of an increased amount of neutral fat in the serum is interesting in connection with the history that the patient drank a glass of milk just after being exposed to vapors of carbon tetrachloride. It is conceivable that the carbon tetrachloride, being an excellent fat solvent, carried more fat into the serum than would ordinarily be present. The carbon tetrachloride was then excreted through the lungs and kidneys, leaving an excess of fat in the serum. In this respect the case is similar to one described by McMahon and Weiss,<sup>7</sup> that of a man who drank carbon tetrachloride in milk and suffered from fat embolism. Butsch<sup>13</sup> also described a high lipid content in his case. Low values for plasma lipids in carbon tetrachloride poisoning were described by Lehnhierr.<sup>42</sup>

The serum phosphatase content was moderately increased, as is often the case when the liver is damaged.

Contrary to the findings of Robbins<sup>43</sup> that carbon tetrachloride is not excreted by the kidneys but only through the lungs in dogs, one must assume that the chemical is at least partly excreted by the kidneys in human beings, in order to explain the renal lesions. However, in human beings with carbon tetrachloride poisoning there is probably also partial excretion through the lungs, which explains the susceptibility of this organ to subsequent infection, as seen in cases 2 and 3.

Minot and Cutler<sup>44</sup> found retention of guanidine in the blood of animals with carbon tetrachloride poisoning and pointed out the similarity between carbon tetrachloride and guanidine poisoning.

Much experimental work (Phelps and Hu,<sup>2</sup> Mauro<sup>11</sup> and others mentioned in the last part of the bibliography) on carbon tetrachloride poisoning has been done with laboratory animals, especially dogs, mainly with regard to hepatic damage and the development of cirrhosis. Since dogs do not excrete carbon tetrachloride through the kidneys,<sup>43</sup> no renal

lesions of consequence have been reported in this animal. The only reference regarding renal lesions in dogs was made by Gardner and his associates,<sup>45</sup> who reported albuminous fluid in almost every glomerular space and some cloudy swelling of the cells of the convoluted tubules. The statement made by Mayer and Pessôa<sup>46</sup> that fatty changes develop in epithelial cells of the convoluted tubules and Henle's loops after the administration of carbon tetrachloride to dogs was contradicted by Schultz and Marx,<sup>47</sup> who found fatty changes in these structures to be a normal feature in this animal.

Although Hall and Shillinger<sup>48</sup> conducted experiments with carbon tetrachloride on cats, they made no mention of renal lesions in their report. Chandler and Chopia,<sup>49</sup> on the other hand, described renal lesions in kittens and cats due to carbon tetrachloride and stated that the renal rather than the hepatic damage was the actual cause of death of their experimental animals. These authors concluded that the susceptibility of this organ in cats accounts for the much greater toxicity of carbon tetrachloride for cats than for dogs. The authors described lesions in the kidneys which were similar to those seen in human beings: degeneration and frequently necrosis of convoluted tubules, with desquamation of lining cells, especially of Henle's loops, infiltration of the capsule of Bowman with blood, and swelling of the glomerular epithelium as well as dilatation of vessels. The urine of these animals always contained albumin and frequently blood.

Mauro<sup>11</sup> conducted inhalation experiments with carbon tetrachloride on rabbits and described cloudy swelling and desquamation of the epithelial cells of the convoluted tubules and of the descending loops of Henle.

An excellent survey of the clinical and pathologic features of acute and chronic intoxication due to carbon tetrachloride in human beings has been given by Smyth<sup>33</sup> and by Smyth, Smyth and Carpenter,<sup>50</sup> who also described renal changes in experimental animals (rats, monkeys and guinea pigs), characterized by swelling, degeneration, necrosis and desquamation of the epithelial cells of the convoluted tubules and the presence of casts in the renal tubules.

On the basis of the work of Minot and Cutler,<sup>41</sup> it may be stated that the symptomatic treatment of carbon tetrachloride poisoning consists of giving calcium carbonate or lactate, dextrose intravenously and infusions of saline or Ringer's solution. Cases of carbon tetrachloride poisoning in which the patients responded to such symptomatic treatment have been reported by Franco,<sup>36</sup> Heyl<sup>37</sup> and others. If carbon tetrachloride is to be given by mouth, alcohol and a fatty diet should be avoided. The administration of carbon tetrachloride is contraindicated in all cases of intestinal obstruction. A high carbohydrate diet is recommended, and the treatment is followed by the administration of saline

cathartic Recently Neale<sup>51</sup> reported the protective action of mono-sodium-2,6-dioxypurine (sodium xanthine) and sodium guanine in experimental carbon tetrachloride poisoning

### CONCLUSIONS

In addition to hepatic damage, carbon tetrachloride poisoning sometimes causes alarming renal symptoms, such as oliguria or anuria, nitrogen retention and subsequent hypertension, the urine contains albumin, white blood cells, red blood cells, casts and bile

The anatomic basis for the clinical renal symptoms is nephrosis characterized by distention of the spaces of Bowman with albuminous precipitate, with swelling of the lining cells, swelling and vacuolation of the cells of the proximal convoluted tubules, degeneration and necrosis of the cells of the distal convoluted tubules and those of the loops of Henle, with desquamation, and by the presence of granular, hyaline and cellular casts in the tubules, with plugging of their lumens. Concretions are present whose nature and significance are obscure

Various clinical and pathologic features of carbon tetrachloride poisoning are discussed

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# Progress in Internal Medicine

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## LIVER AND BILIARY TRACT

A REVIEW FOR 1938

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AND

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NEW YORK

Previous reviews<sup>1</sup> in this series have summarized the clinical and experimental studies concerning the physiology of the gallbladder and biliary tract. The present day treatment and medical management of cholecystitis are based on these physiologic concepts. While many clinical papers have appeared during the past year, the majority have been in accord with these ideas and so do not require specific reference at present. The treatment of hepatic disease was summarized by Greene, Handelsman and Babey<sup>1c</sup> in 1937 and by Snell<sup>2</sup> and Boyce<sup>3</sup> in 1938 and 1939. Reference may be made to these papers for details. At present we wish to summarize recent publications dealing with the etiology of cholelithiasis and certain of the newer developments within the larger field.

### ETIOLOGY OF GALLSTONES

Since the time of Naunyn a mass of clinical and experimental data dealing with gallstones has been accumulated, and a multitude of theories have been propounded to explain the causation of gallstones.

This material has recently been reviewed by Carter, Greene, Twiss and Hotz,<sup>4</sup> who have emphasized the multiplicity and complexity of the

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From the Clinic for the Study of Diseases of the Liver and Biliary Tract of the Department of Medicine and the Department of Surgery of the New York Post-Graduate Medical School and Hospital.

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factors which apparently enter into the formation of biliary calculi. In addition, there are several varieties of gallstones. These authors have suggested that while the factors affecting the formation of gallstones are multiple, they may be divided into two groups. The first group is related to changes in the hepatic bile, while the second is related to changes taking place directly in the gallbladder or bile ducts. These authors have reported on a series of 239 cases, with complete preoperative and postoperative studies, and have investigated the applicability of the various theories in explaining the origin of the stones.

The metabolic theory assumes that disturbances in metabolism so change the hepatic bile as to predispose to the formation of concretions. Giffin,<sup>5</sup> in particular, has emphasized the frequency of gallstones (58 per cent) in adults with congenital hemolytic jaundice. These characteristically are hard, brown or black pigment stones consisting of bilirubin and calcium bilirubinate. They are apparently related to the pleocholia or excessive excretion of bile pigment in this condition. Greene and Snell<sup>6</sup> found experimentally that an augmented rate of excretion of pigment in the bile was brought about primarily by an increase in the concentration rather than by an increase in the volume of the bile. This pleocholia therefore may well predispose to the deposition of this particular form of calculus.

The metabolic theory is usually restricted to the formation of cholesterol stones. As advocated by Chauffard and his co-workers,<sup>7</sup> it assumes a correlation between the concentration of cholesterol in the blood and that in the bile, so maintained that an elevated value for cholesterol in the blood is a predisposing factor in the formation of gallstones. The clinical experience of Chauffard, Moynihan,<sup>8</sup> Hansen,<sup>9</sup> Dewey<sup>10</sup> and others seemingly has substantiated this belief. The observation of an increased concentration of cholesterol in both blood and bile during pregnancy, the frequent onset of clinical symptoms during or immediately after pregnancy and the increased incidence of gallstones in

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5 Giffin, H. Z. Hemolytic Jaundice. A Review of Seventeen Cases, *Surg Gynec & Obst* **25** 152, 1917.

6 Greene, C. H., and Snell, A. M. Studies in the Metabolism of the Bile. II. The Sequence of Changes in the Blood and Bile Following the Intravenous Injection of Bile or Its Constituents, *J Biol Chem* **78** 691, 1928.

7 Chauffard, A., LaRoche, G., and Grigaut, A. Le taux de la cholestérolémie chez les hépatiques, *Compt rend Soc de biol* **70** 20, 1911. Chauffard, A. *Leçons sur la lithiase biliaire*, Paris, Masson & Cie, 1914.

8 Moynihan, B. Some Aspects of Cholelithiasis, *Brit M J* **1** 393, 1925.

9 Hansen, S. Die Bedeutung des Cholesterins für die Bildung von Gallensteinen durch experimentelle Untersuchungen beleuchtet, *Acta chir Scandinav* **62** 383, 1927.

10 Dewey, K. Experimental Hypercholesterolemia. *Arch Int Med* **17** 757 (June) 1916.

women as compared to that in men have all been factors in the acceptance of this theory. Feeding experiments with animals, using diets rich in cholesterol, have demonstrated that the cholesterol content of the blood can be increased markedly by each feeding. This view has received added confirmation by the work of Wilensky<sup>11</sup> and Rothschild and Wilensky<sup>12</sup>. Walsh,<sup>13</sup> Walsh and Ivy,<sup>14</sup> Andrews, Hrdina and Dostal,<sup>15</sup> Riegel, Ravdin and Rose,<sup>16</sup> Patey,<sup>17</sup> and many others, however, could find no such definite relation between the cholesterol content of the blood and that of either the hepatic or the gallbladder bile, either in patients or in experimental animals. Carter, Greene, Twiss and Hotz<sup>4</sup> therefore concluded that there is no direct relation between the cholesterol content of the blood and the formation of gallstones.

The bile salts in hepatic bile are the specific secretion of the hepatic cells, and numerous investigators, notably Stadelmann,<sup>18</sup> Whipple,<sup>19</sup> Ivy,<sup>20</sup> Doubilet,<sup>21</sup> Greene, Walters and Fredrickson,<sup>22</sup> and others, have shown that this excretion in the bile is an extremely sensitive index to the functional activity of the hepatic parenchyma. The bile salts also have a role in keeping the cholesterol of the bile in solution. Changes in the functional activity of the liver from hepatitis, suppression of secretion

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11 Wilensky, A. O. Hypercholesteremia, *Surg., Gynec. & Obst.* **38** 163, 1924.

12 Rothschild, M. A., and Wilensky, A. O. Studies in Cholelithiasis. I. The Disturbances of the Cholesterol Metabolism as a Factor in Gall Stone Formation, *Am. J. M. Sc.* **156** 239, 1918, II. The Chemical Relationships of Cholesterinemia to the Pathological Process, *ibid.* **156** 404, 1918.

13 Walsh, E. L. The Etiology of Gallbladder Calculi, *Arch. Path.* **15** 698 (May) 1933.

14 Walsh, E. L., and Ivy, A. C. Observations on the Etiology of Gall Stones, *Ann. Int. Med.* **4** 134, 1930.

15 Andrews, E., Hrdina, L., and Dostal, L. E. Etiology of Gallstones. II. Analysis of Duct Bile from Diseased Livers, *Arch. Surg.* **25** 1081 (Dec.) 1932.

16 Riegel, C., Ravdin, I. S., and Rose, H. J. Studies of Gallbladder Function. XV. Cholesterol in Human Liver Bile, *J. Clin. Investigation* **16** 67, 1937.

17 Patey, D. H. Modern Views on Mechanism of Formation of Gall Stones, *Brit. M. J.* **1** 866, 1933.

18 Stadelmann, E. *Der Icterus und seine verschiedenen Formen*, Stuttgart, Ferdinand Enke, 1891.

19 Whipple, G. H. Origin and Significance of Constituents of the Bile, *Physiol. Rev.* **2** 440, 1922.

20 Ivy, A. C. Factors Concerned in the Evacuation of the Gall Bladder, *Medicine* **11** 345, 1932.

21 Doubilet, H. Hepatic Excretion in Man of the Various Bile Acids Following Their Oral Administration, *Proc. Soc. Exper. Biol. & Med.* **36** 50, 1937.

22 Greene, C. H., Walters, W., and Fredrickson, C. H. The Composition of the Bile Following the Relief of Biliary Obstruction, *J. Clin. Investigation* **9**. 295, 1930.

or metabolic disturbances may so change the concentration of bile salts in the hepatic bile as to favor the precipitation of cholesterol. The importance of this ratio of bile salts to cholesterol in the formation of gallstones will be discussed presently.

The excretion of bacteria, bile thrombi or abnormal toxic products, due to hepatic damage, and other organic changes in the liver and its secretion have repeatedly been suggested as forming the nuclei for stones. Crile<sup>23</sup> believes that energy changes in the body, affecting the liver and causing abnormality of the bile, result in the formation of stones and that these in turn cause the infection frequently seen in calculous gallbladders. He stated: "Our thesis is that the chemical and physical basis of gall stones is laid by changes in the secretion of the biologically active liver cells and not by changes in the sac that holds and concentrates the bile and performs no other function."

Rous, Drury and McMaster<sup>24</sup> have demonstrated the formation of stones without any evidence of stasis, infection or changes in the composition of the blood. They concluded from this experimental work that stones may form from altered hepatic secretion. Rovsing<sup>25</sup> came to a similar conclusion.

Attempts to show a relation between the intake of fluids and the volume of bile secreted by the liver have been unsuccessful. Of seemingly greater importance are the changes occurring in bile during its passage through the bile ducts and gallbladder. It is here that the controversy concerning the physiology of the gallbladder becomes of major importance in evaluating theories concerning the formation of gallstones. The question is: Does the normal gallbladder absorb cholesterol, as is maintained by Policard,<sup>26</sup> Whitaker,<sup>27</sup> Mentzer,<sup>28</sup> Boyd,<sup>29</sup> Halpert,<sup>30</sup>

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23 Crile, G. Energy Background of Genesis of Gall Stones and of Prevention of Immediate Postoperative Shock and of Later Digestive Disturbances. *Surg., Gynec. & Obst.* **60** 818, 1935.

24 Rous, P., Drury, D. R., and McMaster, P. D. Observations on Some Causes of Gall Stone Formation. II. On Certain Special Nuclei of Deposition in Experimental Cholelithiasis. *J. Exper. Med.* **39** 97, 1924.

25 Rovsing, T. Gall Stones the Cause, Not the Result, of Infection. *Acta chir. Scandinav.* **56** 103, 1923.

26 Policard, A. Sur quelques données histophysiologiques concernant les mecanismes fonctionnels et pathologiques de la vesicule et des voies biliaires. *Lyon chir.* **19** 799, 1922.

27 Whitaker, L. R. The Relation of Biliary Dysfunction to Lithiasis. *New York State J. Med.* **34** 221, 1934.

28 Mentzer, S. H. The Pathogenesis of Biliary Calculi. *Arch. Surg.* **14** 14 (Jan., pt 1) 1927.

29 Boyd, W. Studies in Gall Bladder Pathology. *Brit. J. Surg.* **10** 337, 1923.

30 Halpert, B. The Gallbladder in the Light of Recent Investigation. *Arch. Surg.* **19** 1037 (Dec., pt 1) 1929.

Sweet<sup>31</sup> and others, does it secrete cholesterol, as has been contended by Elman and Graham<sup>32</sup> and as was originally contended by Naunyn,<sup>33</sup> or does it normally only concentrate cholesterol, as indicated by the observations and experimental data of Ravdin and Johnson,<sup>34</sup> Walsh, and Andrews, Schoenheimer and Hrdina<sup>35</sup>? Lichtwitz,<sup>36</sup> in 1914, further complicated the question by suggesting that cholesterol saturation of the plicae of the gallbladder, by absorption from the bile, and their subsequent delinescence formed the nuclei for "metabolic stones." Though this concept has been supported more recently by Gosset, Bertrand and Lœwy,<sup>37</sup> it has been denied by Illingworth<sup>38</sup> and Mackey<sup>39</sup>.

It is generally agreed that the gallbladder extracts water, sodium chloride and other inorganic salts from the hepatic bile, concentrating it from seven to ten times (Ravdin and Johnson<sup>34</sup> and others). It appears from clinical and experimental studies that while the mucosa of the gallbladder may absorb bile salts or cholesterol from the bile, this does not occur under normal circumstances. In the presence of an inflammation, when the mucosa is edematous, Dostal and Andrews<sup>40</sup> have shown that bile salts are rapidly absorbed by the wall of the gallbladder. Clinically this is seen most readily in cases of hydrops of the gallbladder. Another explanation, advanced by Rous and McMaster,<sup>41</sup> is that bile, including cholesterol and bile salts, is replaced by mucus which is a specific

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31 Sweet, J. E. The Formation of Gallstones, *Am J Surg* **40** 162, 1938

32 Elman, R., and Graham, E. A. Pathogenesis of "Strawberry" Gallbladder (Cholesterosis of the Gallbladder), *Arch Surg* **24** 14 (Jan) 1932

33 Naunyn, B. *Klinik der Cholelithiasis*, Leipzig, F. C. W. Vogel, 1892, A Treatise on Cholelithiasis, translated by A. E. Garrod, London, New Sydenham Society, 1896, *Die Gallensteine Ihre Entstehung und ihr Bau*, Jena, Gustav Fischer, 1921

34 Ravdin, I. S., and Johnson, C. G. The Gall Bladder. Recent Advances as Applied to Treatment, *Pennsylvania M J* **35** 357, 1932

35 Andrews, E., Schoenheimer, R., and Hrdina, L. Etiology of Gallstones. Chemical Factors and Role of the Gallbladder, *Arch Surg* **25** 796 (Oct) 1932

36 Lichtwitz, L. Ueber die Bildung der Harn und Gallensteine, *Ergebn d inn Med u Kinderh* **13** 1, 1914

37 Gosset, A., Bertrand, I., and Lœwy, G. La vesicule fraise, *Progres med* **44** 1792, 1928

38 Illingworth, C. F. W. Cholesterosis of the Gall Bladder. A Clinical and Experimental Study, *Brit J Surg* **17** 203, 1929

39 Mackey, A. Cholesterosis of the Gall Bladder, *Brit J Surg* **24** 570, 1937

40 Dostal, L. E., and Andrews, E. Etiology of Gallstones. Effect of Diet on the Bile Salt-Cholesterol Ratio, *Arch Surg* **26** 258 (Feb) 1933

41 Rous, P., Drury, D. R., and McMaster, P. D. Observations on Some Causes of Gall Stone Formation. II. On Certain Special Nuclei of Deposition in Experimental Cholelithiasis, *J Exper Med* **39** 97, 1924

response of the mucosa of the gallbladder Aronsohn and Andrews<sup>42</sup> have demonstrated that chemical cholecystitis may be set up by a high concentration of bile salts in the gallbladder and possibly in the blood stream How then can one account for the concentration of cholesterol which may be found in gallbladder bile—100 to 2,000 mg per hundred cubic centimeters? The hepatic bile contains little cholesterol, and yet ten to a hundred times this concentration is often seen in the gallbladder at operation, whereas the bile salt concentration is seldom above seven to ten times the concentration in the hepatic bile While this finding may be cited as evidence that the cholesterol is secreted by the mucosa of the gallbladder, the work of Boyd, Whitaker, Sweet, and Wilkie and Doubilet<sup>43</sup> opposes such an assumption

It is agreed that some if not all of the cholesterol in the bile is in a state of colloidal solution The studies of Wieland and Sorge<sup>44</sup> showed that the bile salts, particularly the salts of desoxycholic acid, form addition compounds with fatty acids or cholesterol which increase the solubility of the cholesterol Verzar,<sup>45</sup> in particular, has stressed the importance of such compounds in favoring the intestinal absorption of lipoids and cholesterol Other investigators, following Newman,<sup>46</sup> have stressed the importance of these compounds in keeping the cholesterol in the bile in solution and have insisted that when the ratio of bile salts to cholesterol falls below a critical level, cholesterol is precipitated out of solution It is further assumed that such precipitation leads to the formation of cholesterol calculi

The bile salt-cholesterol ratio may be disturbed either by hepatic damage with a changed hepatic bile or by a differential absorption of cholesterol and bile salts in the gallbladder or bile ducts Hammarsten<sup>47</sup> reported the bile salt-cholesterol ratio in normal gallbladders to be 25 : 1 Newman, who first emphasized the importance of this ratio in

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42 Aronsohn, H. G., and Andrews, E. Experimental Cholecystitis, *Surg., Gynec. & Obst.* **66** 748, 1938

43 Wilkie, A. L., and Doubilet, H. Passage of Cholesterol Through the Mucosa of the Gallbladder, *Arch. Surg.* **26** 110 (Jan.) 1933

44 Wieland, H., and Sorge, H. Untersuchungen über die Gallensauren, *Ztschr. f. physiol. Chem.* **97** 1, 1916

45 Verzar, F., and von Kuthy, A. Die Bedeutung der Gallensauren für die Fettresorption (Arbeiten über Resorption), *Biochem. Ztschr.* **205** 369, 1929  
Verzar, F. Die Bedeutung der gepaarten Gallensauren für die Fettresorption, *ibid.* **230** 451, 1931, Absorption of Fats, *Nutrition Abstr. & Rev.* **2** 441, 1933

46 Newman, C. Physiology of the Gall Bladder and Its Functional Abnormalities, *Lancet* **1** 785 and 896, 1933

47 Hammarsten, O. Zur Chemie der Galle, *Ergebn. d. Physiol.* **4** 1, 1905, *Text-Book of Physiological Chemistry*, ed. 5, translated by J. A. Mandel, New York, J. Wiley & Sons, 1906

the pathogenesis of gallstones, stated that the critical ratio for the precipitation of cholesterol is 18 : 1. Andrews, Schoenheimer and Hrdina have placed the critical ratio at 13 : 1.

Carter, Greene, Twiss and Hotz found that in their cases the bile salt-cholesterol ratio was highly variable and that the difference between the ratios in cases of calculous and of noncalculous gallbladders was not sufficient to account for the stones. Chabrol, Cottet and Cachin<sup>48</sup> have suggested that the bile salt-cholesterol ratio may well be disturbed by the factors causing the gallstones more frequently than it is the cause of the latter. Walsh and Ivy, Walsh, and Dolkart, Jones and Brown,<sup>49</sup> in exhaustive experimental studies, have shown that fatty acids have a markedly solvent action on cholesterol masses and on "mixed gallstones." They believe therefore that it is the concentration of fatty acids in the bile rather than that of bile salts that keeps the cholesterol in solution. Illingworth, Reinhold, Ferguson and Hunsberger,<sup>50</sup> and Weiser and Gray,<sup>51</sup> on the other hand, do not attach significance to the presence of fatty acids, for they were unable to demonstrate fatty acids in bile from normal gallbladders in sufficient concentration to prevent the precipitation of cholesterol.

Phemister and his associates<sup>52</sup> have reported that precipitates of calcium salts are formed in the gallbladder only when complete obstruction and low grade chronic inflammation are present. They believe that since cholesterol is not found in such gallbladders, the gallbladder cannot be the source of the cholesterol found in gallstones. Calcium salts, they believe, represent a specific response on the part of the wall of an inflamed gallbladder.

Reported changes in the reaction of bile have not been consistently demonstrated in calculous gallbladders. Feldman, Morrison and

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48 Chabrol, E., Cottet, J., and Cachin, M. Recherches sur le rôle respectif du cholestérol et de l'acide cholalique dans la pathogénie de la lithiase biliaire, *Ann de med* **42** 607, 1937.

49 Dolkart, R. E., Jones, K. K., and Brown, C. F. G. The Relation of the Hydrogen Ion Concentration of Bile to the Formation of Gall Stones, *Am J Digest Dis & Nutrition* **4** 587, 1937, Chemical Factors Concerned in the Formation of Gallstones, *Arch Int Med* **62** 618 (Oct.) 1938.

50 Reinhold, J. G., Ferguson, L. K., and Hunsberger, A. Composition of the Human Gall Bladder Bile and Its Relationship to Cholelithiasis, *J Clin Investigation* **16** 367, 1937.

51 Weiser, H. B., and Gray, G. R. Mechanism of the Formation of Pure Cholesterol Gallstones, *Arch Path* **17** 1 (Jan.) 1934.

52 Phemister, D. B., Day, L., and Hastings, A. B. Calcium Carbonate Gallstones and Their Experimental Production, *Ann Surg* **96** 595, 1932. Phemister, D. B., Aronson, H. G., and Pepinski, R. Variations in Cholesterol, Bile Pigment, and Calcium Salts Contents of Gallstones Formed in Gallbladder and in Bile Ducts with the Degree of Associated Obstruction, *ibid* **109** 161, 1939.

Krantz,<sup>53</sup> reasoning from the observation that human cholesterol and "mixed gallstones" will dissolve when placed in the more acid gallbladder bile of a dog, believe that the alkaline  $p_H$  found in human hepatic bile, unchanged by the gallbladder, may be an important etiologic factor in the formation of gallstones. Reinhold, Ferguson and Hunsberger, Reinhold and Ferguson,<sup>54</sup> Rous,<sup>55</sup> and Weiser and Gray, on the other hand, did not find that the normal gallbladder bile had a higher hydrogen ion concentration than hepatic bile, nor do they believe that there is any marked change in the presence of an inflammation. Walsh reported that an acid  $p_H$  allows cholesterol to stay in solution more readily, but he ascribed this to the presence of bile acids and to fatty acids, which are known solvents of cholesterol. Dolkart, Jones and Brown found no statistically significant difference in the relative solvent action upon mixed stones of acid and of alkaline bile secured from the ox, the dog and man.

The original hypothesis of Naunyn, propounded in 1892, held that gallstones are the result of infection in the gallbladder or bile ducts. Nearly all subsequent theories have presupposed that some injury, inflammation or chemical change of the bile in the gallbladder is the initiating cause for the formation of stones. As Sir Berkeley Moynihan has stated, "The gall stone is a tombstone erected to the memory of the organism within it." The early clinical researches indicated that most gallbladders with stones were infected. Gordon-Taylor and Whitby<sup>56</sup> found 70 per cent infected, Moynihan found 95 per cent infected and Walton<sup>57</sup> found 70 per cent infected. Various recent clinical studies have shown a wide variation in the incidence of positive results of culture in cases of calculous gallbladders. Moynihan, Griffith and Kipp,<sup>58</sup>

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53 Feldman, M., Morrison, S., and Krantz, J. C. Etiology of Gall Stones. Relationship of  $p_H$  of Bile to Formation and Dissolution of Gall Stones, *Am J Digest Dis & Nutrition* 4 13, 1937. Feldman, M., Morrison, S., Carr, C. J., and Krantz, J. C. Etiology of Gall Stones. Hydrogen Ion Concentration of Gall Bladder Bile and Its Effects upon Gall Stones, *ibid* 4 223, 1937.

54 Reinhold, J. G., and Ferguson, L. K. Reaction of Human Bile and Its Relationship to Gall Stone Formation, *J Exper Med* 49 681, 1929.

55 Rous, P. Physiological Factors in the Genesis of Gall Stones, *Proc Inst Med Chicago* 7:33, 1928.

56 Gordon-Taylor, G., and Whitby, L. E. H. A Bacteriological Study of Fifty Cases of Cholecystectomy with Special Reference to Anaerobic Infections, *Brit J Surg* 18 78, 1930.

57 Walton, J. The Formation and Treatment of Calculi in the Biliary Ducts and Gall Bladder, *Surg, Gynec & Obst* 64 257 1937.

58 Griffith, J. P., and Kipp, H. A. Remarks on the Etiology and Treatment of Cholecystitis, *Pennsylvania M J* 35 362, 1932.



Patey, Walton, Albeaux-Fernet,<sup>59</sup> and Walters,<sup>60</sup> as well as many others, are certain, from a clinical point of view, that infection of the gallbladder is a basic cause for the formation of stones, infection causing changes in the mucosa with resulting functional disturbances, stasis and colloidal changes favoring precipitation. All are in agreement that pure cholesterol stones are metabolic in origin and differ thus from mixed or common gallstones. Potter and Mann,<sup>61</sup> Illingworth, Ravdin and Johnson, and Furth<sup>62</sup> have reached the same general conclusion after animal experimentation as well as clinical studies. Illingworth believes that the Lichtwitz theory of electropositive and electronegative charges, with the inflammatory exudate acting as an electronegative substance, may explain the "trigger mechanism" which causes the cholesterol to precipitate.

Aschoff and Bacmeister,<sup>63</sup> Rovsing and Crile, after both clinical and experimental studies, on the other hand, believe that the infection is the consequence and not the cause of gallstones. MacCarty<sup>64</sup> made a statistical study of 21,523 gallbladders but was unable to determine which was the prior factor, whereas Walters, and Ravdin and Johnson believe either may be the initial condition. Carter, Greene, Twiss and Hotz have pointed out that it is debatable whether this question can be answered by clinical research alone. In only 33 per cent of the cases which they classified as cases of "early cholecystitis" with or without stones was there either bacteriologic or pathologic evidence of inflammation or infection. In 24 cases gallstones were present, but there was no pathologic or bacteriologic evidence of inflammation or infection. This group of cases they considered as evidence that infection is not necessary for the formation of stones and as presumptive evidence that the formation of stones may precede infection of the gallbladder.

The assumption of Aschoff and Bacmeister that infection or the products of infection are not the cause of stones arose from their experimental and clinical studies on the precipitation of cholesterol in the presence of stasis within the gallbladder. They maintained that this stasis, regardless of the cause, favored changes in solubility due to over-

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59 Albeaux-Fernet, M. Les hypothèses pathogéniques de la lithiase biliaire, *Gaz med de France (supp Gastro-enterol)* [43] 3, 1936.

60 Walters, W. Pathological Physiology of Stone in the Common Duct. Clinical and Surgical Significance, *Surg, Gynec & Obst* 63 417, 1936.

61 Potter, J. C., and Mann, F. C. Pressure Changes in the Biliary Tract, *Am J M Sc* 171 202, 1926.

62 Furth, O. Pathologische Physiologie der Steinbildung, *Wien klin Wchnschr* 50 68, 1937.

63 Aschoff, L., and Bacmeister, A. Die Cholelithiasis, Jena, Gustav Fischer, 1909. Aschoff, L. Lectures on Pathology, New York, Paul B. Hoeber, 1924.

64 MacCarty, W. C. The Gallbladder and Its Diseases, *Proc Staff Meet, Mayo Clin* 11 805, 1936.

concentration of the cholesterol with resultant precipitation. The precipitated cholesterol was the nucleus of stones. The fact that many pathologic conditions, as well as some that are neurogenic in origin, result in biliary stasis and an increased concentration of the bile within the gallbladder has been established by Westphal,<sup>65</sup> Ivy, Whitaker, and Greene, Twiss and Carter<sup>66</sup> McMaster and Elman,<sup>67</sup> Boyden,<sup>68</sup> Whitaker, and Ravdin and Johnson could demonstrate no definite reciprocal relation between the sphincter of Oddi and the gallbladder of dogs. According to Berg and Jobling,<sup>69</sup> Ivy and Mentzer, there is much indirect evidence that such a relation does exist.

Whitaker has demonstrated the formation of pseudostones in the gallbladder of dogs by inducing stasis in the absence of infection or hepatic damage. Mentzer, von Babarczy<sup>70</sup> and Halpert have also made a strong case for stasis. Ravdin and Johnson, Walters, Walsh, Moore<sup>71</sup> and Rous have shown that stasis is at least an accessory factor in stone formation. Copher and Illingworth<sup>72</sup> were unable to reproduce Whitaker's experiments and so agree with Pavel,<sup>73</sup> Furth and many others that stasis probably is not a cause for the formation of gallstones.

The observation that pure cholesterol stones may crystallize according to the laws of colloids has led to the colloidal theory of stone formation,

65 Westphal, K. Muskelfunktion, Nervensystem und Pathologie der Gallenwege, *Ztschr f klin Med* **96** 22, 1933, Die Bewegungs- und Resorptionsstörungen an den Gallenwegen und ihre Gefahren, *Verhandl d deutsch Gesellsch f inn Med*, Kong 44, 1932, p 354

66 Greene, C H, Twiss, J R, and Carter, R F. Biliary Stasis, *Am J Digest Dis & Nutrition* **3** 622, 1936

67 McMaster, P D, and Elman, R. On the Expulsion of Bile by the Gall Bladder and a Reciprocal Relationship with the Sphincter Activity, *J Exper Med* **44** 173, 1926

68 Boyden, E A. Sphincter of Oddi in Man and Certain Representative Mammals, *Surgery* **1** 25, 1937

69 Berg, B N, and Jobling, J W. The Effect of Division and Transplantation of the Common Duct upon the Gall-Bladder Function, *Proc Soc Exper Biol & Med* **24** 434, 1927. Berg, B N. Gall Bladder Function After Division of the Common Duct, *Surg, Gynec & Obst* **46** 464, 1927

70 von Babarczy, M. Die Bedeutung des Cholesterins in der Diätetik der Cholecystopathien, *Ztschr f klin Med* **133** 656, 1938

71 Moore, S W. Intramural Formation of Gallstones, *Arch Surg* **34** 410 (March) 1937

72 Copher, G H, and Illingworth, C F W. Experimental Study of the Factor of Biliary Stasis in the Production of Gall Stones, *Surg, Gynec & Obst.* **46** 658, 1928

73 Pavel, I. Du rôle peu important de la stase dans la pathogénie de la lithiase biliaire (avec une critique de la dyskinésie et quelques considérations thérapeutiques), *Presse méd* **43** 1565, 1935

supported extensively by Sweet,<sup>74</sup> Weiser and Gray, and Schade<sup>75</sup> Sweet has maintained that "under normal conditions, whatever passes into the gallbladder through the cystic duct, never passes out again through the cystic duct" He found synthetic stones made from gelatin, chromates and silver nitrate to be structurally similar to the cholesterol stones in the human gallbladder The Liesegang phenomena, with rhythmic precipitation of calcium and pigment, he thinks, explain the laminated appearance on section of cholesterol and mixed gallstones Phemister, on the other hand, has insisted that the deposition of calcium is evidence of inflammatory changes in the wall of the gallbladder When a gallstone consists of a central nucleus of cholesterol with several rings of calcium and pigment around the periphery, Phemister and others have insisted that this structure is evidence for the occurrence of successive attacks of obstruction and active cholecystitis in a gallbladder which initially contained a pure cholesterol stone of metabolic origin At present these opposing views of Phemister and Sweet are irreconcilable

Pancreatic ferments have been found in many calculous gallbladders removed at operation, and it has been assumed that the ferments were regurgitated up the common and cystic ducts into the gallbladder Sweet, Crile, and Wolfer<sup>76</sup> believe this may be a factor leading to the precipitation of cholesterol Colp, Gerber and Doubilet<sup>77</sup> believe such a reflux was the cause of severe acute cholecystitis seen in 3 cases which they reported Aronsohn and Andrews<sup>78</sup> were able markedly to change the bile salt-cholesterol ratio in the gallbladders of dogs by injecting pancreatic fluid into them Cartei, Greene, Twiss and Hotz have suggested that the common finding of pancreatic ferments in gallbladders removed at operation warrants further investigation, for their data were inconclusive This is particularly important if the observation of

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74 Sweet, J E (a) The Liesegang Phenomenon in Gall Stones, in Colloid Symposium Annual Papers Presented at the Seventh Symposium on Colloid Chemistry at Johns Hopkins University in June 1929, New York, 1930, p 249, (b) Formation of Calculi, *Ann Surg* **103** 67, 1936

75 Schade, H Zur Entstehung der Harnsteine und ähnlicher konzentrisch geschichteter Steine organischen und anorganischen Ursprungs, *Ztschr f Chem u Indust d Kolloide* **4** 175, 1909, cited by Sweet<sup>74b</sup>

76 Wolfer, J A Further Evidence That Pancreatic Juice Reflux May Be the Etiologic Factor in Gallbladder Disease, *Ann Surg* **109** 187, 1939

77 Colp, R, Gerber, L C, and Doubilet, H Acute Cholecystitis Associated with Pancreatic Reflux, *Ann Surg* **103** 67, 1936

78 Aronsohn, H G, and Andrews, E Experimental Cholecystitis, *Surg, Gynec & Obst* **66** 748, 1938

Mehnen<sup>79</sup> is confirmed that the frequency of gallstones is greatest in those cases in which the anatomic structure of the papilla of Vater favors the regurgitation of pancreatic juice into the gallbladder

Carter, Greene, Twiss and Hotz have pointed out that their study served to emphasize the difficulty of determining the causation and pathogenesis of gallstones solely by study of the patient at the time of operation. If the deposition of a calculus depends on the concomitant action of several different factors, then the period of calculous formation may be limited in extent, and a study of the patient one to twenty-five years later will fail to present the true picture of the conditions determining the deposition of the stone. It must also be recognized that the different types of gallstones may differ as to causation. When the various theoretic factors advanced as possible causes of gallstones were studied, these authors found no single factor or combination of factors which satisfactorily explained the origin of gallstones. In their series of cases, stasis was the only one of the factors considered that could be demonstrated in 25 per cent of the cases of gallstones. They consider this presumptive evidence that stasis is of importance in the formation of gallstones, but they have pointed out that other unknown factors must also be in operation, for stasis was found in the majority of the noncalculous gallbladders as well.

#### SERUM PHOSPHATASE IN JAUNDICE

In the review for 1937<sup>1d</sup> reference was made to a series of papers by Thannhauser and his associates<sup>80</sup> reporting that ascorbic acid activates the serum phosphatase. Theoretic conclusions regarding the cause and significance of the increase in serum phosphatase in jaundice were drawn on the basis of these observations. During the past year,

79 Mehnen, H. Die Bedeutung der Mundungsverhältnisse von Gallen- und Pankreasgang für die Entstehung der Gallensteine, *Arch f klin Chir* **192** 559, 1938

80 Thannhauser, S. J., Reichel, M., and Grattan, J. F. Studies on Serum Phosphatase Activity. I. Ascorbic Acid Activation on Serum Phosphatase, *J Biol Chem* **121** 697, 1937. Thannhauser, S. J., Reichel, M., Grattan, J. F., and Maddock, S. II. The Effect of Experimental Total Biliary Obstruction on the Serum Phosphatase Activation in Dogs and Cats, *ibid* **121** 709, 1937, III. The Effect of Complete Biliary Fistula on Phosphatase Activation in Dogs and Cats, *ibid* **121** 697, 1937, IV. The Deactivating Effect of Thiol Compounds and Bile Acids on Serum Phosphatase in Vitro and in Vivo, *ibid* **121** 720, 1937, V. Studies Concerning Increased Serum Phosphatase Values in Disease, *ibid* **121** 727, 1937. Maddock, S., Thannhauser, S. J., Reichel, M., and Grattan, J. F. A New Conception of Serum Phosphatase. A Review of Experimental Work, *New England J Med* **218** 166, 1938.

King and Delory<sup>81</sup> reported that they were unable to confirm Thannhauser's basic observations regarding the effect of ascorbic acid on phosphatase activity. Thannhauser, Reichel and Grattan<sup>82</sup> then repeated their earlier work and found that when solutions of ascorbic acid and beta glycerophosphate were allowed to stand, the glycerophosphate was hydrolyzed. In their earlier experiments this spontaneous hydrolysis was misinterpreted as evidence of activation of the phosphatase. Thannhauser, Reichel and Grattan therefore abandoned their theory that ascorbic acid activates the serum phosphatase.

Thannhauser, Reichel, Grattan and Maddock<sup>83</sup> have not abandoned their interpretation of the cause for the increased serum phosphatase value in jaundice. They have made reference to the observation of Freeman and Chen<sup>84</sup> that when a normal dog is given a transfusion of normal blood, there is no change in the serum phosphatase level, when blood from a dog with obstructive jaundice is given, the serum phosphatase level of the recipient invariably rises to a high level and remains unchanged during the course of the acute experiment. In some cases it did not return to normal by the eighth day after the transfusion. Thannhauser and his associates<sup>83</sup> also reported experiments in which serum from a dog with jaundice was mixed with normal serum in vitro. The phosphatase activity of the mixture was greater than that calculated from the phosphatase activity of the original serums. They therefore reiterated their original contention that in cases of jaundice the serum contains a substance that will activate the phosphatase in normal serum.

Clinical experience in the use of the serum phosphatase value in the differential diagnosis of jaundice, as reported by Giordano, Wilhelm and Prestrud,<sup>85</sup> confirms the previous contention of Greene, Shattuck and Kaplowitz<sup>86</sup> that this is not a dependable diagnostic procedure.

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81 King, E. J., and Delory, G. E. Ascorbic Acid and Phosphatase Activity, *Biochem J* **32** 1157, 1938.

82 Thannhauser, S. J., Reichel, M., and Grattan, J. F. The Effect of Ascorbic Acid on  $\beta$ -Glycerophosphate, *Biochem J* **32** 1163, 1938.

83 Thannhauser, S. J., Reichel, M., Grattan, J. F., and Maddock, S. J. Studies on Serum Phosphatase Activity. VI. The Influence of Sera with High Phosphatase Activity on Normal Sera, *J Biol Chem* **124** 631, 1938.

84 Freeman, S., and Chen, Y. P. The Effect of Jaundiced Blood upon Normal Dogs, with Special Reference to the Serum Phosphatase, *J Biol Chem* **123** 239, 1938.

85 Giordano, A. S., Wilhelm, A., and Prestrud, M. C. The Serum Phosphatase in the Differential Diagnosis of Obstructive Jaundice, *Am J Clin Path* **9** 226, 1939.

86 Greene, C. H., Shattuck, H. F., and Kaplowitz, L. The Phosphatase Content of the Blood Serum in Jaundice, *J Clin Investigation* **13** 1079, 1934.

## SULFANILAMIDE AND THE LIVER

The past two years have witnessed the introduction of a new chemotherapeutic agent for the treatment of hemolytic streptococcal infection. Sulfanilamide is now accepted by the medical profession, and its therapeutic value is generally recognized. The clinical literature dealing with its use is voluminous and will not be reviewed here, as this has been done in part by Colebrook and Kenny,<sup>87</sup> Colebrook, Buttle and O'Meara,<sup>88</sup> Long and Bliss,<sup>89</sup> Marshall, Emerson and Cutting,<sup>90</sup> Ottenberg,<sup>91</sup> and many others.

The earlier clinical and experimental reports indicated that exceedingly large doses were necessary to produce toxic effects in either animals or man. It was a surprise, therefore, in September and October 1937 when a series of deaths supposedly due to poisoning by sulfanilamide were reported.<sup>92</sup> There were over a hundred finally reported, which were traced to poisoning by elixir of sulfanilamide (Massengill).<sup>93</sup> The patients complained of nausea, abdominal cramps, dizziness, malaise and vomiting. This was followed by oliguria and anuria. The patients became drowsy and had slight jaundice in some instances. They became progressively comatose and died in uremic coma.<sup>94</sup>

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87 Colebrook, L., and Kenny, M. Treatment of Human Puerperal Infections and of Experimental Infections in Mice with Prontosil, *Lancet* **1** 1279, 1936.

88 Colebrook, L., Buttle, G. H. A., and O'Meara, R. A. Q. Mode of Action of *p*-Aminobenzenesulphonamide and Prontosil in Hemolytic Streptococcal Infections, *Lancet* **2** 1323, 1936.

89 Long, P. H., and Bliss, E. A. Para-Amino-Benzene-Sulfonamide and Its Derivatives. Experimental and Clinical Observations on Their Use in the Treatment of Beta-Hemolytic Streptococcal Infection, Preliminary Report, *J. A. M. A.* **108** 32 (Jan 2) 1937, Clinical Use of Sulfanilamide, *Ann. Int. Med.* **11** 575, 1937.

90 Marshall, E. K., Jr., Emerson, K., Jr., and Cutting, W. C. Para-aminobenzenesulfonamide. Absorption and Excretion, Method of Determination in Urine and Blood, *J. A. M. A.* **108** 953 (March 20) 1937.

91 Ottenberg, R. The Treatment of Hemolytic Streptococcus Infections and the Newer Applications of Sulphanilamide, *Bull. New York Acad. Med.* **14** 453, 1938.

92 Elixir of Sulfanilamide-Massengill. II, report of the Chemical Laboratory, *J. A. M. A.* **109** 1724 (Nov 20) 1937. Deaths Due to Elixir of Sulfanilamide-Massengill. Report of Secretary of Agriculture Submitted in Response to House Resolution 352 of Nov 18, 1937, and Senate Resolution 194 of Nov 16, 1937, *ibid.* **109** 1985 (Dec 11) 1937.

93 Deaths Following Elixir of Sulfanilamide-Massengill, editorial, *J. A. M. A.* **109** 1367 (Oct 23) 1937.

94 Ruprecht, H. A., and Nelson, I. A. Clinical and Pathologic Observations, *J. A. M. A.* **109** 1537 (Nov 6) 1937. Hagebusch, O. E. Necropsies of Four Patients Following Administration of Elixir of Sulfanilamide-Massengill, *ibid.* **109** 1537 (Nov 6) 1937. Lynch, K. M. Diethylene Glycol Poisoning in the Human, *South. M. J.* **31** 134, 1938.

The principal pathologic changes were in the kidneys and liver<sup>95</sup>. The former showed chemical nephrosis, with enlargement, the development of cortical necrosis and hydropic degeneration of the epithelium of the convoluted tubules. The liver was enlarged and was described as tawny, although not bile stained, with pale, soft surfaces which bulged after sectioning. Sections showed extensive focal central hydropic degeneration of the hepatic cells without any marked inflammatory reaction.

Chemical analysis indicated that the preparation was essentially a 10 per cent solution of sulfanilamide in 72 per cent diethylene glycol<sup>96</sup>. Pharmacologic analysis<sup>97</sup> showed that the chief toxic agent in this elixir of sulfanilamide was the diethylene glycol and not the sulfanilamide. In fact, the characteristic pathologic lesions in the liver and spleen could not be produced by administration of sulfanilamide alone.

Clinical observation of patients receiving sulfanilamide has indicated that the most frequent toxic effect is the development of cyanosis<sup>98</sup>. This usually is mild and disappears rapidly after withdrawal of the drug.

Harvey and Janeway, Kohn, and Jennings and Southwell-Sanders<sup>99</sup> were among the first to report the occasional development of severe hemolytic anemia in association with sulfanilamide therapy. This anemia is readily controlled by withdrawal of the drug and the giving of a transfusion. In a few cases, as reported by Ottenberg and by Lockwood, Coburn and Stokinger<sup>100</sup> and in 1 case observed by us,

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95 Cannon, P. R. Pathologic Effects Following the Ingestion of Diethylene Glycol, Elixir of Sulfanilamide-Massengill, "Synthetic" Elixir of Sulfanilamide and Sulfanilamide Alone, *J. A. M. A.* **109** 1536 (Nov. 6) 1937.

96 Schoeffel, E. W., Kreider, H. R., and Peterson, J. B. Chemical Examination of Elixir of Sulfanilamide-Massengill, *J. A. M. A.* **109** 1532 (Nov. 6) 1937.

97 Geiling, E. M. K., Coon, J. M., and Schoeffel, E. W. Preliminary Report of Toxicity Studies on Rats, Rabbits, and Dogs Following Ingestion in Divided Doses of Diethylene Glycol, Elixir of Sulfanilamide-Massengill, and "Synthetic" Elixir, *J. A. M. A.* **109** 1532 (Nov. 6) 1937. Geiling, E. M. K., and Cannon, P. R. Pathologic Effects of Elixir of Sulfanilamide (Diethylene Glycol) Poisoning. A Clinical and Experimental Correlation, Final Report, *ibid.* **111** 919 (Sept. 3) 1938.

98 Descombe, G. Sulfhemoglobinemia Following Sulfanilamide Treatment, *Lancet* **1** 626, 1937.

99 Harvey, A. M., and Janeway, C. A. The Development of Acute Hemolytic Anemia During the Administration of Sulfanilamide (Para-Aminobenzenesulfonamide), *J. A. M. A.* **109** 12 (July 3) 1937. Kohn, S. E. Acute Hemolytic Anemia During Treatment with Sulfanilamide, *ibid.* **109** 1005 (Sept. 25) 1937. Jennings, G. M., and Southwell-Sanders, G. Anemia and Agranulocytosis During Sulfanilamide Therapy, *Lancet* **2** 898, 1937.

100 Lockwood, J. S., Coburn, A. F., and Stokinger, H. E. Studies on the Mechanism of the Action of Sulfanilamide. I. The Bearing of the Character of the Lesion on the Effectiveness of the Drug, *J. A. M. A.* **111** 2259 (Dec. 17) 1938.

the hemolytic anemia was sufficiently rapid in onset and marked in intensity to produce associated acute hemolytic jaundice. Fortunately, all these patients recovered without untoward incident.

Jaundice as a result of toxic hepatitis is an equally rare complication of sulfanilamide therapy. Hageman and Blake,<sup>101</sup> Saphirstein<sup>102</sup> and Long<sup>103</sup> have each reported a case of acute hepatitis. Garvin<sup>104</sup> has reported 5 cases with 1 death. Bannick, Brown and Foster<sup>105</sup> have reported 2 fatal cases, while Cline<sup>106</sup> has reported a case of acute yellow atrophy of the liver following sulfanilamide medication. We have observed 2 similar cases and a third which ended fatally but in which the lapse of a month between the administration of sulfanilamide and the development of jaundice made it difficult to determine the relation of the drug to the final outcome.

One of us observed another patient who while under treatment with sulfanilamide for hemolytic streptococcal septicemia suddenly showed severe jaundice. This therapy was discontinued, but the patient died within five days. At necropsy the liver was markedly enlarged, smooth and engorged. There was no extrahepatic obstruction of the biliary tract. Microscopic examination revealed focal periportal degeneration without leukocytic infiltration. The pathologic picture was that of acute toxic hepatitis. Chemical examination of the hepatic tissue showed 6 mg of sulfanilamide per hundred grams as against a concentration of 1 to 1.5 mg per hundred grams in tissue from the lungs. This single case suggests a specific affinity of sulfanilamide for the liver. It is by no means certain that the death described was directly due to sulfanilamide, but a contributory role is evident.

The majority of toxic manifestations which appear in the course of treatment with sulfanilamide apparently develop on the basis of sensitivity or idiosyncrasy. The cases that have just been cited indicate

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101 Hageman, P. O., and Blake, F. G. A Specific Febrile Reaction to Sulfanilamide. Drug Fever, *J. A. M. A.* **109** 642 (Aug. 28) 1937.

102 Saphirstein, H. Hepatitis and Toxic Erythema with Desquamation Due to Sulfanilamide, *Urol. & Cutan. Rev.* **42** 101, 1938.

103 Long, P. H. The Clinical Use of Sulfanilamide and Its Derivatives, with Special Reference to Their Possible Toxic Effects, *Ohio State M. J.* **34** 977, 1938.

104 Garvin, C. F. Toxic Hepatitis Due to Sulfanilamide, *J. A. M. A.* **111** 2283 (Dec. 17) 1938.

105 Bannick, E. F., Brown, A. E., and Foster, F. P. Therapeutic Effectiveness and Toxicity of Sulfanilamide and Several Related Compounds. Further Clinical Observations, *J. A. M. A.* **111** 770 (Aug. 27) 1938.

106 Cline, E. W. Acute Yellow Atrophy of the Liver Following Sulfanilamide Medication, *J. A. M. A.* **111** 2384 (Dec. 24) 1938.



that, while such manifestations are infrequent, nevertheless there are cases in which sulfanilamide is capable of causing severe hepatic damage

There is evidence that sulfanilamide, instead of being harmful, may in selected cases be of value in the treatment of infections of the liver and biliary tract. We have found, as have Ottenberg and Berck<sup>107</sup> and Crile,<sup>108</sup> that sulfanilamide is excreted in the bile after oral administration. Ottenberg and Berck also reported 2 cases of suppurative pylephlebitis and hepatic abscess in which recovery followed sulfanilamide therapy. In view of the almost hopeless character of such conditions, the further trial of this type of therapy is desirable.

#### VITAMIN K AND BLOOD COAGULATION

Clotting is the most striking and best known property of blood, but there is little agreement among physiologists as to the mechanism of this phenomenon. The available evidence indicates that the clotting of blood apparently involves two consecutive reactions. The first is the interaction between the prothrombin in the plasma, calcium and platelets (or tissue extract) to form thrombin. The second is the reaction between thrombin and fibrinogen with the formation of fibrin. Any attempt at further analysis of this phenomenon, as pointed out in the recent reviews of Howell<sup>109</sup> and Eagle,<sup>110</sup> leads the investigator into a maze of contradictory and often mutually exclusive theories.

The bleeding tendency which may develop in the patient with jaundice has long been recognized. The explanation, on the other hand, has been a source of controversy, as is demonstrated by the historical summaries presented by Moss,<sup>111</sup> Lewisohn,<sup>112</sup> Judd, Snell and Hoerner,<sup>113</sup> Ivy, Shapiro and Melnick,<sup>114</sup> and others. It is now accepted that the resorption of bile is without direct effect on the

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107 Ottenberg, R, and Berck, M. Sulfanilamide Therapy for Suppurative Pylephlebitis and Liver Abscess, *J A M A* **111** 1374 (Oct 8) 1938

108 Crile, G, Jr. Recent Advances in the Treatment of Obstructive Jaundice, *Cleveland Clin Quart* **6** 116, 1939

109 Howell, W H. Theories of Blood Coagulation, *Physiol Rev* **15** 435, 1935

110 Eagle, H. Recent Advances in the Blood Coagulation Problem, *Medicine* **16** 138, 1937

111 Moss, W. Experimental Obstructive Jaundice. Its Effect on Fibrinogen and Coagulation of the Blood, *Arch Surg* **26** 1 (Jan) 1933

112 Lewisohn, R. Haematologic Studies as a Basis for Determining the Risk of Post-Operative Hemorrhage in Jaundice Patients, *Ann Surg* **94** 80, 1931

113 Judd, E S, Snell, A M, and Hoerner, M T. Transfusion for Jaundiced Patients, *J A M A* **105** 1653 (Nov 23) 1935

114 Ivy, A C, Shapiro, P F, and Melnick, P. The Bleeding Tendency in Jaundice, *Surg, Gynec & Obst* **60** 781, 1935

coagulation of the blood The concentration of bilirubin, bile salts or cholesterol in the blood in jaundice bears no relation to the disturbance in the coagulability of the blood Calcium deficiency, if present, ordinarily does not determine the tendency toward hemorrhage The amount of fibrinogen, as shown by Lewisohn,<sup>112</sup> Ham and Curtis,<sup>115</sup> Moss and others, is rarely diminished in jaundice Barlik<sup>116</sup> postulated the presence of interfering substances in the nature of antithrombin or antiprothrombin, and Carr and Foote<sup>117</sup> tried to characterize them chemically, but this work has not been confirmed Howell suggested that heparin may be responsible for the normal fluidity of the blood, but this view is not accepted, and thus far there has been no evidence indicating an increase in the concentration of heparin in the blood in jaundice

Recent investigators have agreed that a decrease in the amount of prothrombin in the plasma is the most probable explanation of the hemorrhagic tendency in jaundice This was suggested by the studies of Lewisohn, Bancroft, Kugelmass and Stanley-Brown,<sup>118</sup> Nygaard,<sup>119</sup> and Quick, Stanley-Brown and Bancroft<sup>120</sup> and has been confirmed by Warner, Brinkhous, and Smith,<sup>121</sup> Boyce and McFetridge,<sup>122</sup> Quick,<sup>123</sup> and others in cases of jaundice

Slight reductions in the prothrombin content of the blood have little effect on the coagulation of blood The coagulation time, as measured by the usual methods, shows but little increase until more than 80 per cent of the prothrombin is lost Any reduction below this critical

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115 Ham, T H, and Curtis, F C Plasma Fibrinogen Response in Man Influence of the Nutritional State, Induced Hyperpyrexia, Infectious Disease and Liver Damage, *Medicine* **17** 413, 1938

116 Barlik, A Ueber das Wesen der verzögerten Blutgerinnung beim Stauungsikterus, *Arch f klin Chir* **176** 252, 1933

117 Carr, J L, and Foote, F S Progressive Obstructive Jaundice Changes in Certain Elements of the Blood and Their Relation to Coagulation, *Arch Surg* **29** 277 (Aug) 1934

118 Bancroft, F W, Kugelmass, N, and Stanley-Brown, M Evaluation of Blood Clotting Factors in Surgical Disease, *Ann Surg* **90** 161, 1929

119 Nygaard, K K Coagulability of Blood Plasma A Method of Determining the Hemorrhagic Tendency of Jaundiced Patients, *Proc Staff Meet, Mayo Clin* **7** 691, 1932

120 Quick, A J, Stanley-Brown, M, and Bancroft, F W A Study of the Coagulation Defect in Hemophilia and Jaundice, *Am J M Sc* **190** 501, 1935

121 Warner, E D, Brinkhous, K M, and Smith, H P A Quantitative Study on Blood Clotting Prothrombin Fluctuations Under Experimental Conditions, *Am J Physiol* **114** 667, 1936

122 Boyce, F F, and McFetridge, E M A Serum Volume Test for the Hemorrhagic Diathesis in Jaundice, *J Lab & Clin Med* **23** 202, 1937

123 Quick, A J The Nature of the Bleeding in Jaundice, *J A M A* **110** 1658 (May 14) 1938

level, on the other hand, is accompanied by a marked disturbance in the clotting mechanism. This observation explains why a patient with prothrombin deficiency may show no tendency to hemorrhage before operation, but when the prothrombin content of the blood is further reduced by the trauma of operation, the hemorrhagic tendency may become manifest in fatal form. Fortunately, the converse is also true, and only a slight increase in the prothrombin content of the blood may suffice to control the hemorrhagic tendency. The beneficial effects of transfusion probably are to be explained on such a basis.

Not only do patients with jaundice show a reduction in the prothrombin content of the blood, but Smith, Warner and Brinkhous<sup>124</sup> and Quick have found that similar changes occur in experimental animals after injury to the liver from chloroform or carbon tetrachloride. Changes in the prothrombin content of the blood have also been noted independently of hepatic injury. Farmers have noted a hemorrhagic tendency in stock fed on sweet clover hay which has been spoiled during curing. Roderick<sup>125</sup> noted that there was prothrombin deficiency in this condition, his investigations have been extended by Quick<sup>126</sup>.

Dam and Schönheyder<sup>127</sup> in Denmark and Almquist and Stokstad<sup>128</sup> in this country discovered that a hemorrhagic disease could be produced in chicks by means of a diet deficient in a new food accessory. Dam named this the "koagulation vitamin" or vitamin K. Dam and his co-workers<sup>129</sup> and later Quick found that the blood of chicks suffering from a deficiency of vitamin K was deficient in prothrombin. Feeding of vitamin K in the form of green vegetables, extracts of

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124 Smith, H. P., Warner, E. D., and Brinkhous, K. M. Prothrombin Deficiency and the Bleeding Tendency in Liver Injury (Chloroform Intoxication), *J. Exper. Med.* **66** 801, 1937.

125 Roderick, L. M. A Problem in the Coagulation of the Blood. Sweet Clover Disease of Cattle, *Am. J. Physiol.* **96** 413, 1913. Roderick, L. M., and Schalk, A. F. Studies on Sweet Clover Disease, *Bulletin, North Dakota Agricultural Experiment Station*, 1931.

126 Quick, A. J. The Coagulation Defect in Sweet Clover Disease and in the Hemorrhagic Chick Disease of Dietary Origin, *Am. J. Physiol.* **118** 260, 1937.

127 Dam, H., and Schönheyder, F. A Deficiency Disease in Chicks Resembling Scurvy, *Biochem. J.* **28** 1355, 1934, The Occurrence and Chemical Nature of Vitamine "K," *ibid.* **30** 897, 1936.

128 Almquist, H. J., and Stokstad, E. L. R. Hemorrhagic Chick Disease of Dietary Origin, *J. Biol. Chem.* **11** 105, 1935.

129 Dam, H. The Antihemorrhagic Vitamin of the Chick, *Biochem. J.* **29** 1273, 1935. Schönheyder, F. The Quantitative Determination of Vitamin K, *ibid.* **30** 890, 1936. Dam, H., Schönheyder, F., and Tage-Hansen, E. Studies on the Mode of Action of Vitamin K, *ibid.* **30** 1075, 1936. Dam, H., and Schönheyder, F. Vitamin K, *Nord. med. tidskr.* **12** 1097, 1936.

alfalfa, fish meal or several vegetable oils cured the hemorrhagic tendency in chicks and restored the prothrombin value to normal

Almquist,<sup>130</sup> Almquist and Stokstad<sup>131</sup> and Ansbacher<sup>132</sup> have reported attempts to secure concentrated preparations of vitamin K, and Thayer and his associates<sup>133</sup> have reported the isolation of a crystalline product from alfalfa leaves that is very active in restoring the clotting time of the blood of hemorrhagic chicks to normal. Lichtman and Chambers<sup>134</sup> more recently have reported the isolation of an active clotting factor from the liver

In 1936 Greene<sup>1b</sup> discussed the importance of bile for the absorption of fats and of vitamin A. Since then Greaves and Schmidt<sup>135</sup> have published a series of reports indicating the importance of bile to the absorption of the various fat-soluble vitamins, carotene and vitamins D and E. Hawkins and Whipple<sup>136</sup> reported the development of a hemorrhagic tendency in dogs with an experimentally produced biliary fistula. Hawkins and Brinkhous<sup>137</sup> and Greaves and Schmidt<sup>138</sup> showed that this was due to a deficiency of prothrombin in the blood. It can be corrected by feeding either bile or vitamin K. Similar results have been reported in experimental obstructive jaundice

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130 Almquist, H. J. Purification of the Antihemorrhagic Vitamin, *J Biol Chem* **114** 241, 1936, Chemical and Physical Studies on the Antihemorrhagic Vitamin, *ibid* **117** 517, 1937, Further Studies on the Antihemorrhagic Vitamin, *ibid* **120** 635, 1937

131 Almquist, H. L., and Stokstad, E. L. R. Factors Influencing the Incidence of Dietary Hemorrhagic Disease in Chicks, *J Nutrition* **12** 329, 1936

132 Ansbacher, S. New Observations on the Vitamin K Deficiency of the Chick, *Science* **88** 221, 1938

133 Thayer, S. A., MacCorquodale, D. W., Binkley, S. B., and Doisy, E. A. The Isolation of a Crystalline Compound with Vitamin K Activity, *Science* **88** 243, 1938

134 Lichtman, A. L., and Chambers, W. H. Reduced Blood Coagulation Time by the Injection of Sterol Extract of Liver, *Science* **88** 358, 1938

135 Greaves, J. D., and Schmidt, C. L. A. Rôle Played by Bile in Absorption of Vitamin D in the Rat, *J Biol Chem* **102** 101, 1933, Studies on the Vitamin A Requirements of the Rat, *Am J Physiol* **116** 456, 1936, Relation of Certain Bile Acids to the Absorption of Beta-Carotene in the Rat, *Proc Soc Exper Biol & Med* **36** 434, 1937, Relation of Bile to Absorption of Vitamin E in the Rat, *ibid* **37** 40, 1937

136 Hawkins, W. B., and Whipple, G. H. Bile Fistulas and Related Abnormalities, Bleeding, Osteoporosis, Cholecystitis and Duodenal Ulcer, *J Exper Med* **62** 599, 1935

137 Hawkins, W. B., and Brinkhous, K. M. Prothrombin Deficiency the Cause of Bleeding in Bile Fistula Dogs, *J Exper Med* **63** 795, 1936

138 Greaves, J. D., and Schmidt, C. A. L. Nature of the Factor Concerned in the Loss of Blood Coagulability of Bile Fistula Rats, *Proc Soc Exper Biol & Med* **37** 43, 1937. Greaves, J. D. The Nature of the Factor Which Is Concerned in the Loss of Blood Coagulability of Bile Fistula and Jaundiced Rats. *Am J Physiol* **125** 423, 1939

Clinical and experimental evidence therefore is in agreement that the hemorrhagic tendency seen in cases of obstructive jaundice or of biliary fistula is related to a deficiency of prothrombin in the blood. The maintenance of a normal prothrombin value is determined by the presence in the food of an adequate supply of vitamin K and in the bowel of sufficient bile to insure the proper absorption of vitamin K. The role of the liver is less well understood, though the prothrombin content of the blood is decreased after experimental hepatic injury and in some cases of cirrhosis and severe hepatitis.

The clinical application of these findings has been made in a number of laboratories. Preparations of bile or bile salts<sup>139</sup> as well as viosterol were administered to jaundiced patients empirically with occasional benefit before the role of either prothrombin or vitamin K was understood.

Extracts of fish meal or alfalfa or other substances rich in vitamin K have been administered to jaundiced patients with consequent increase in the prothrombin content of the blood and reduction in the hemorrhagic tendency. Warner, Brinkhous and Smith,<sup>140</sup> Butt, Snell and Osterberg,<sup>141</sup> Dam and Glavind,<sup>142</sup> Brinkhous, Smith and Warner,<sup>143</sup> Snell, Butt and Osterberg,<sup>144</sup> Ravdin,<sup>145</sup> Walters,<sup>146</sup> and Olson and Menzel<sup>147</sup> agree that the oral administration of vitamin K and bile salts in both the preoperative preparation and the postoperative care

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139 McNealy, R W, Shapiro, P F, and Melnick, P. The Effect of Viosterol in Jaundice, *Surg, Gynec & Obst* **60** 785, 1935. Johnson, C G. Preoperative and Post-Operative Treatment of Cases of Obstructive Jaundice, *Surgery* **3** 875, 1938.

140 Warner, E D, Brinkhous, K M, and Smith, H P. Bleeding Tendency of Obstructive Jaundice. Prothrombin Deficiency and Dietary Factors, *Proc Soc Exper Biol & Med* **37** 628, 1938.

141 Butt, H R, Snell, A M, and Osterberg, A E. The Use of Vitamin K and Bile in Treatment of the Hemorrhagic Diathesis in Cases of Jaundice, *Proc Staff Meet, Mayo Clin* **13** 74, 1938.

142 Dam, H, and Glavind, J. Vitamin K in Human Pathology, *Lancet* **1** 720, 1938.

143 Brinkhous, K M, Smith, H P, and Warner, E D. Prothrombin Deficiency and the Bleeding Tendency in Obstructive Jaundice and in Biliary Fistula. Effect of Feeding Bile and Alfalfa (Vitamin K), *Am J M Sc* **196** 50, 1938.

144 Snell, A M, Butt, H R, and Osterberg, A E. Treatment of the Hemorrhagic Tendency in Jaundice with Especial Reference to Vitamin K, *Am J Digest Dis* **5** 590, 1938.

145 Ravdin, I S, in discussion on Snell, Butt and Osterberg<sup>144</sup>

146 Walters, W. Lesions of the Extrahepatic Biliary Tract, *J A M A* **11** 2477 (Dec 31) 1938.

147 Olson, K B, and Menzel, H. The Bleeding Tendency in Obstructive Jaundice and Its Control by Means of Vitamin K, *Surgerv*, to be published.

of jaundiced patients is effective in preventing and controlling the hemorrhagic diathesis of these patients

This procedure, while largely empiric, nevertheless represents a real therapeutic advance and deserves a more intensive clinical use. Snell, Butt and Osterberg have recommended the oral administration of 1 to 4 Gm of animal bile salts and 0.4 to 1.2 Gm of alfalfa concentrate daily. Olson and Menzel used 4 Gm of bile salts and 1,000 units of vitamin K daily for from two to seven days.

At present the commercially available preparations of vitamin K must be given orally or administered through a duodenal tube, as they are not suitable for parenteral administration. Dam and his associates<sup>148</sup> have reported the successful intramuscular use of purified concentrate of vitamin K, but Butt, Snell and Osterberg<sup>149</sup> found that their preparations were not as effective in reducing the prothrombin time after intramuscular injection as was the same quantity given by mouth. When crystalline preparations of vitamin K become available, it may be possible to develop efficacious methods of parenteral administration.

The past year has seen the introduction of "blood banks" in many hospitals<sup>150</sup> in this country. "Bank blood" which has been stored for three to ten days is satisfactory for transfusion in the great majority of cases. Rhoads and Panzer<sup>151</sup> and Olson and Menzel have recently demonstrated that there is a rapid fall in the prothrombin content of "bank blood." These reports, while not substantiated by clinical cases, nevertheless imply that after the first day or so "bank blood" would be of little value in overcoming the bleeding tendency of the jaundiced patient. Earlier surgical experience, as summarized by Judd, Snell and Hoerner, indicated that transfusion was the most effective method then available of controlling this tendency to bleeding. The recent work on the prothrombin content of the blood has indicated that the improvement following transfusion is short lived and much inferior to the effect produced by the administration of preparations of vitamin K.

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148 Dam, H., and Glavind, J. The Clotting Power of Human and Mammalian Blood in Relation to Vitamin K, *Acta med Scandinav* **96** 108, 1938. Dam, H., Glavind, J., Lewis, L., and Tage-Hansen, E. Studies on the Mode of Action of Vitamin K, *Scandinav Arch f Physiol* **79** 121, 1938.

149 Butt, H. R., Snell, A. M., and Osterberg, A. E. Further Observations on the Use of Vitamin K in the Prevention and Control of the Hemorrhagic Diathesis in Cases of Jaundice, *Proc Staff Meet, Mayo Clin* **13** 753, 1938.

150 Fantus, B., and Schirmer, E. H. The Therapy of the Cook County Hospital Blood Preservation Technic, *J A M A* **111** 317 (July 23) 1938. Cameron, C. S., and Ferguson, L. K. The Operation and Technique of the Blood Bank at the Philadelphia General Hospital, *Surgery* **5** 237, 1939.

151 Rhoads, J. E., and Panzer, L. M. The Prothrombin Time of "Bank Blood," *J A M A* **112** 309 (Jan 28) 1939.

and bile salts. In consequence, the number of transfusions given for the control of the hemorrhagic tendency in jaundiced patients is likely to be reduced markedly in the future.

### SPHEROCYTIC JAUNDICE

Diseases of the spleen are of especial interest to both internist and surgeon because of the position of this organ as an integral part of the hemopoietic system, on the one hand, and its association with the liver on the other. Hemolytic jaundice is an example of a condition in which both these relations of the spleen are affected.

A special clinic for the study of splenopathies was organized at the Columbia Medical Center<sup>152</sup> several years ago, and the investigators have begun to report on the results of their studies.

Thompson,<sup>153</sup> as part of this study of 55 cases of hemolytic jaundice, has pointed out that the term hemolytic jaundice is used clinically in all cases in which there is evidence of jaundice and anemia due to increased destruction of the red blood cells. The spleen usually is enlarged and the number of reticulocytes in the blood increased. Thompson, however, has reemphasized the fact that cases of this clinical syndrome should be divided into two separate groups.

Minkowski<sup>154</sup> was the first to establish congenital hemolytic jaundice as a clinical entity. Chauffard,<sup>155</sup> in 1907, discovered the markedly increased fragility of the erythrocytes in hypotonic salt solution and a year later reported the presence of reticulated red blood cells in large numbers.<sup>156</sup> Haden<sup>157</sup> further demonstrated that the microcytosis was due to the presence in the blood of a variable proportion of spherical erythrocytes which were smaller in diameter than normal. It is these smaller cells which are alone responsible for the fragility in this condition. This spherocytosis apparently represents a congenital defect in the red blood cells. Krumbhaar<sup>158</sup> therefore has suggested the term spherocytic jaundice for this condition.

152 Whipple, A. O. The Medical-Surgical Splenopathies, *Bull. New York Acad. Med.* **15** 174, 1939.

153 Thompson, W. P. Hemolytic Jaundice. Its Diagnosis, Behavior and Treatment, *Bull. New York Acad. Med.* **15** 177, 1939.

154 Minkowski, O. Ueber eine hereditäre, unter dem Bilde eines chronischen Icterus mit Urobilinurie, Splenomegalie und Nierensiderosis verlaufende Affection, *Verhandl. d. deutsch. Kongr. f. inn. Med.* **18** 316, 1900.

155 Chauffard, A. Pathogenie de l'ictère congénital de l'adulte, *Semaine med.* **27** 25, 1907.

156 Chauffard, A. Les ictères hemolytiques, *Semaine méd.* **28** 49, 1908.

157 Haden, R. L. Mechanism of Increased Fragility of Erythrocytes in Congenital Hemolytic Jaundice, *Am. J. M. Sc.* **188** 441, 1934.

158 Krumbhaar, E. B. Modern Concepts of Anemia from the Clinical Standpoint, *Bull. New York Acad. Med.* **13** 501, 1937.

Summarizing the knowledge of this condition, Thompson has pointed out that it is a chronic disease of long duration and relative mildness, though acute exacerbations may occur. The presenting symptom is usually chronic variable jaundice. Splenomegaly is the outstanding feature on physical examination. Anemia may be mild or severe, and in cases of latent spherocytic jaundice the blood count may be normal. The degree of jaundice and the degree of reticulocytosis are both variable but tend to be proportional to the degree of anemia. The peripheral blood contains spherocytes, which may be recognized directly and counted by examination of wet film preparations or measured indirectly by determination of the fragility in hypotonic salt solution.

Spherocytes constitute 10 to 25 per cent of the total number of erythrocytes. They not only are present in the blood of all patients with clinically recognizable forms of the disease but may also be found in their relatives in whom the condition is latent. These spherical cells are selectively removed from the circulation by the spleen. That they are actively destroyed there is suggested by the observation of Kaznelson,<sup>159</sup> Rich and Rienhoff,<sup>160</sup> Greene and Conner,<sup>161</sup> and Thompson that in these cases blood from the splenic vein contains more bilirubin than blood from the splenic artery.

Indirect evidence of the activity of the spleen in destruction of these cells is afforded by the rapid disappearance both of the jaundice and of the evidence of increased hemolysis following splenectomy. That the spherocytes persist in the blood in undiminished numbers after splenectomy is further evidence that the beneficial effect of splenectomy is due to the cessation of a hemolytic process and not to the return of erythropoiesis to normal.

Transfusion is the accepted method of treatment for the anemia associated with spherocytic jaundice,<sup>162</sup> especially during a hemoclastic

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159 Kaznelson, P. Beitrag zur Entstehung des hemolytischen Ikterus, *Wien Arch f inn Med* **1** 563, 1920.

160 Rich, A. R., and Rienhoff, W. F., Jr. The Bile-Pigment Content of the Splenic Vein, *Bull Johns Hopkins Hosp* **36** 431, 1925.

161 Greene, C. H., and Conner, H. M. Diseases of the Liver. V. A Comparative Study of Tests for Hepatic Function in Certain Diseases of the Hematopoietic System, *Arch Int Med* **38** 167 (Aug.) 1926.

162 Tileston, W. Hemolytic Jaundice, *Medicine* **1** 355, 1922. Cheney, W. F., and Cheney, G. Chronic Hereditary Jaundice, *Am J M Sc* **187** 191, 1934. Bazin, A. T. Splenectomy. Operative Procedure and After-Care, *Canad M A J* **33** 482, 1935. Hurxthal, L. M. Hemolytic Jaundice. Consideration of the Diagnosis and Treatment, *S Clin North America* **15** 1475, 1935. Dudley, G. S. Familial Hemolytic Jaundice, *ibid* **16** 839, 1936.



crisis and immediately before splenectomy Loid Dawson<sup>163</sup> and Hartfall and Stewart<sup>164</sup> have reported cases in which a fatal reaction occurred after a transfusion Baker and Dodds,<sup>165</sup> Wise<sup>166</sup> and Sharpe and Davis<sup>167</sup> have reported severe reactions in patients who were given a transfusion while in a state of acute hemoclastic crisis Doan, Wiseman and Elf<sup>168</sup> are of the opinion that a transfusion, with the addition of red blood cells, only furnishes more material for hemolysis, with further pigmentary and toxic embarrassment to both the liver and the kidneys Dawson concluded that the reaction and subsequent deaths in his cases were due to blocking of the renal tubules with masses of acid hematin pigment

DeGowin, Osterhagen and Andersch<sup>169</sup> have given a clue to the prevention of such a reaction by their experimental studies on dogs in which they found that hemoglobin was innocuous in large amounts when the urine was alkaline but was precipitated in the renal tubules when the urine was acid Witt<sup>170</sup> has practiced alkalization of the urine in such cases before transfusion From these findings it appears that transfusion in the presence of a severe hemoclastic crisis is dangerous and to be avoided Should transfusion be considered imperative, thorough alkalization of the urine may prevent a severe reaction or a fatality

In marked contrast to the cases of spherocytic jaundice are the cases of atypical hemolytic jaundice The condition may be acquired as the result of the administration of specific toxic substances, as in the cases of acute hemolytic jaundice associated with sulfanilamide therapy which have been discussed There are also cases of idiopathic jaundice in which, as Thompson has pointed out, the mechanism is not understood at present and in which splenectomy is of no benefit

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163 Dawson, B E Hemolytic Jaundice, *Brit M J* **1** 921 and 963, 1931

164 Hartfall, S J, and Stewart, M J Massive Paravertebral Heterotopia of Bone-Marrow in a Case of Acholuric Jaundice, *J Path & Bact* **37** 455, 1933

165 Baker, S L, and Dodds, E C Obstruction of the Renal Tubules During the Excretion of Hemoglobin, *J Path & Bact* **6** 247, 1925

166 Wise, W D Hemolytic Jaundice, *Am J Surg* **20** 722, 1933

167 Sharpe, J C, and Davis, H H Severe Reactions Following Transfusions in Hemolytic Jaundice, *J A M A* **110** 2053 (June 18) 1938

168 Doan, C A, Wiseman, B K, and Elf, L A Studies in Hemolytic Jaundice, *Ohio State M J* **30** 493, 1934

169 DeGowin, E L, Osterhagen, H F, and Andersch, M Renal Insufficiency from Blood Transfusion Relation to Urinary Acidity, *Arch Int Med* **59** 432 (March) 1937, Grave Sequels to Transfusion Clinical Study of Thirteen Cases Occurring in Three Thousand and Five Hundred Transfusions, *Ann Int Med* **11** 1777, 1938

170 Witt, L J A Note on Blood Transfusions, *Lancet* **1** 1297, 1929

## CIRRHOSIS OF THE LIVER

During the past year Bloomfield<sup>171</sup> has had occasion to survey the natural history of chronic hepatitis and to reemphasize that cirrhosis of the liver usually is the terminal stage of chronic hepatitis of long duration. This conception is not new, but it usually has not been emphasized or the evidence on which it rests has not been, as here, brought forward in "a round unvarnished tale." He has pointed out in his study of 41 cases that the early course of the disease usually is run without clinical symptoms. Only about 10 per cent of his patients gave a history of a previous attack of jaundice, so that he concluded that acute hepatitis with jaundice rarely is the initial stage or precursor of cirrhosis. That latent hepatitis may exist for long periods without concomitant symptoms was shown by 2 patients in each of whom a firm, enlarged liver and splenomegaly were incidental discoveries. These patients continued to be free from symptoms for several years but finally died with the characteristic clinical picture of portal cirrhosis nine and eleven years, respectively, after the first examination.

In 3 cases the clinical history suggested that the process began with an initial attack of acute hepatitis which ran a rapid progressive course, with the development of the picture of cirrhosis within a few months. In a considerable number of cases, however, it was impossible to decide whether the patient was first seen because of acute hepatitis or because of an acute exacerbation occurring in the course of a chronic and previously latent hepatitis.

These cases reported by Bloomfield therefore lend support to the idea that hepatic cirrhosis represents the end stage of chronic hepatitis, with progressive injury to the liver either from a chronic, slowly progressive disease or from the effect of repeated exacerbation of such a disease. This idea is in harmony with the experimental finding, noted in the review of Moon,<sup>172</sup> that the histologic picture of cirrhosis may be produced in animals by the repeated administration over a prolonged period of such hepatotoxins as carbon tetrachloride, copper and phosphorus.

Recent experimental studies have emphasized the importance of diet in relation to the symptoms of cirrhosis. Bollman<sup>173</sup> has reported the daily administration of carbon tetrachloride to a series of dogs on differ-

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171 Bloomfield, A. L. The Natural History of Chronic Hepatitis (Cirrhosis of the Liver), *Am J M Sc* **195** 429, 1938.

172 Moon, V. H. Experimental Cirrhosis in Relation to Human Cirrhosis, *Arch Path* **18** 381 (Sept) 1934, *Experimentelle Lebercirrhose und ihre Beziehungen zur Aetologie der menschlichen Cirrhose*, *Klin Wchnschr* **13** 1489 and 1521, 1934.

173 Bollman, J. L. Some Experimental Observations Pertinent to the Treatment of Hepatic Disease, *Ann Int Med* **12** 1, 1938.

ent diets The 4 animals receiving a diet of 80 per cent fat and 10 per cent each of carbohydrate and protein were all dead within three weeks In each case the liver was enlarged and fatty and showed numerous areas of degeneration Two of the animals which received only lean meat died within three months, and the other 2 had definite ascites The dogs on diets of 50 per cent carbohydrate and 25 per cent each of fat and protein and the ones on diets with 90 per cent carbohydrate were in good condition six to eight months later

Bollman further found that alcohol was without effect on the livers of dogs receiving a well balanced diet though given twice daily to the stage of intoxication for more than two years In fasting animals or those on diets rich in fat the livers became fatty, and the administration of alcohol greatly increased the rapidity of this change Animals with such fatty livers showed marked sensitization to the toxic effects of carbon tetrachloride

The relation of the liver to the metabolism of fat and the extensive recent literature on experimental studies of fatty infiltration of this organ were reviewed in 1937 These studies originated in the observation of Fisher<sup>174</sup> and of Allan, Bowie, Macleod and Robinson<sup>175</sup> that depancreatized dogs treated with insulin in adequate dosage nevertheless had marked fatty infiltration of the liver which eventually resulted in death Chaikoff, Connor and Biskind<sup>176</sup> have extended these observations and have shown that after four or five years the livers of these animals presented the picture of well advanced portal cirrhosis They considered that the sequence of events was fatty infiltration, hyaline degeneration and atrophy of the cells at the periphery of the lobules and then orderly fibroblastic proliferations, ending with the typical appearance and fibrotic structure of cirrhosis

The cause of the fatty infiltration of the liver in the depancreatized dog has been a source of controversy It can be prevented by the feeding of raw pancreas Best, Ferguson and Hershey<sup>177</sup> showed that it could be prevented by feeding lecithin or choline and consider that the latter is the active principle in the pancreas Dragstedt, Van Plohaska and

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174 Fisher, N F Attempts to Maintain the Life of Totally Pancreatectomized Dogs, *Am J Physiol* **67** 634, 1924

175 Allan, F N , Bowie, D J , Macleod, J J R , and Robinson, W L Behavior of Depancreatized Dogs Kept Alive with Insulin, *Brit J Exper Path* **5** 75, 1924

176 Chaikoff, I L , Connor, C L , and Biskind, G R Fatty Infiltration and Cirrhosis of the Liver in Depancreatized Dogs Maintained with Insulin, *Am J Path* **14** 101, 1938

177 Best, E H , Ferguson, G C , and Hershey, J M Choline and Liver Fat in Diabetic Dogs, *J Physiol* **79** 94, 1933

Harms<sup>178</sup> prepared another extract from the pancreas, which they called the lipocaic hormone. When fed to dogs, this material prevented fatty infiltration of the liver. They consider that "lipocaic" is a specific hormone of the pancreas. The latter view has been denied by Best and Ridout,<sup>179</sup> who have insisted that the lipotropic effect of "lipocaic" in their hands could be explained by the lipotropic effect predicted from its choline and protein content. This subject is still a matter of controversy but serves to emphasize the importance of diet in its relation to fatty infiltration of the liver.

Connor<sup>180</sup> has continued the clinical application of these studies and has reviewed the literature dealing with fatty infiltration of the liver in its relation to the development of cirrhosis in diabetes and in chronic alcoholism. He has pointed out that

Fatty infiltration of the liver occurs in those conditions where, because of lack of intake or absorption of food, fat is mobilized from the existing fat depots, and where, because of internal interference with the metabolism of fat due to anoxemia or tissue anoxia, the accumulated fat cannot be broken down for use. In the first instance it results from external starvation, in the second from what may be called internal or tissue starvation. In both instances normal carbohydrate-fat metabolism does not take place. Among the conditions in which this normal metabolism is altered or inhibited are the various diseases which, by their nature, are called wasting, the disease diabetes, and that following the introduction of poisons which inhibit proper tissue oxidation, the most common of which is alcohol.

In the starvation accompanying progressive morbid states the condition is of little pathological importance, being in most cases terminal in nature. In diabetes the enlarged fatty liver may be influenced by insulin and by strict dieting, but also may persist for many years. In alcoholism a variety of factors operate to produce the same condition. Alcohol alone will cause some fatty infiltration, but as relative and sometimes absolute starvation is constantly associated with severe chronic alcoholism, the development of fatty infiltration of the liver most often depends on a combination of these two. The absence of vitamin B<sup>1</sup> in the diet may contribute to this also, but such deficiency is probably of minor importance. An analysis of existing recorded observations and experiments, indicate that a liver containing demonstrable neutral fat is in most cases pathological, that fat may pass into and out of the liver with astonishing rapidity, and that fat may be present in such amounts as to interfere seriously with both the metabolic and the mechanical functions of the organ. The development of perilobular fibrosis seems to be

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178 Dragstedt, L. R., Van Prohaska, J., and Harms, H. P. Observations on a Substance in the Pancreas Which Permits Survival and Prevents Liver Changes in Depancreatized Dogs, *Am J Physiol* **117** 175, 1936.

179 Best, C. H., and Ridout, J. H. The Pancreas and the Deposition of Fat in the Liver, *Am J Physiol* **122** 67, 1938.

180 Connor, C. L. Fatty Infiltration of the Liver and the Development of Cirrhosis in Diabetes and Chronic Alcoholism, *Am J Path* **14** 347, 1938, The Etiology and Pathogenesis of Alcoholic Cirrhosis of the Liver, *J A M A* **112** 387 (Feb 4) 1939.

the result of a combination of mechanical pressure, local tissue anoxia and general anoxemia, causing atrophy and degeneration of liver cells

The alcoholic liver occurs in two forms, one of which is the precursor of the other. The first is the enlarged tense liver so swollen with fat that the distended surface lobules present the appearance of cirrhosis. This effect is further simulated by the intrahepatic block, which interferes with excretion of bile, and the transmission of portal blood. The clinical signs of jaundice and ascites are thus produced. Many such patients lapse into coma and die, and at autopsy the large liver is the only prominent finding. These show lobules distended with fat and some show, in addition, hyaline degeneration and atrophy of peripheral cells associated with early proliferation of fibroblasts.

A series of cases reported by Connor represented this form, and another series illustrated the second form, in which further proliferation of connective tissue produced the typical picture of portal cirrhosis as seen in chronic alcoholism. An unmistakable gradation of the one into the other is so manifest that the mechanism of the production of alcoholic cirrhosis seems to Connor to have been demonstrated. The absence of fat in many such livers at the end is explained by the exhaustion of body fat, by the discontinuance of the consumption of alcohol and by the resumption of a normal or a high carbohydrate diet.

Connor has further reported that from a study of a large number of cases composite pictures may be assembled to illustrate three phases of the disease of the liver produced by alcohol. The three phases occur at the ages of about 40 to 45, 50 to 55 and 50 to 65, respectively, the ages overlapping as would be expected from the nature of the disease. When it is understood that the first acute stage may be reached in from six months to two years, the second in from one to five years and the third in from two to twenty years or more, it can be seen how unreliable age statistics are. The age is usually above 40, because men usually do not begin to drink the quantity of alcohol necessary to produce these changes until after that age.

The acute fatty liver of alcoholism develops after the prolonged use of very large amounts of alcohol during which little or no food is taken or the food consists of protein and fat only. It is found in men picked up by the police who die shortly afterward in prison or in city hospitals. It is most common in the coroner's morgues in all large cities. When the patient lives long enough for clinical examination he may show signs of cirrhosis, such as jaundice and some ascites, but has a large liver. The liver is pale and greasy, containing about 60 per cent fat. It may be lobulated because of the severe swelling but is usually smooth. Because of the swelling there also may be intrahepatic obstruction of the bile ducts, giving a green coloration, and portal obstruction without fibrosis. Such livers are recognized by all medical examiners as evidence of alcoholism and as being associated generally with poor nutrition. The deaths of patients in this stage "represent the inevitable mortality

during the experimental production of cirrhosis in man" The others pass on to the next stage

The fatty liver in which there is early but definite and progressing perlobular fibrosis is the product of alcoholism which is less in degree than that causing the first phase but which is nevertheless severe. In the liver which survives drastic alcohol poisoning and a partial starvation diet, a fibrous tissue stroma will develop in the course of time. The liver is large or of normal weight and moderately lobulated or smooth. It is sclerotic, it may not be bile stained and it produces classic early signs and symptoms of cirrhosis. The condition is the common fatty cirrhosis of the liver found in most classifications.

The liver in the third phase is likely to be somewhat reduced in size and to have a nodular surface and a thickened capsule. It never becomes as small as the liver of toxic cirrhosis, seldom weighing under 1,300 Gm. Fat may or may not be present. The condition follows the long-continued use of excessive amounts of alcohol by a person who has continued to take a better diet, but as to both alcohol and diet the habits have been abnormal. There may have been intermittent severe episodes of drinking lasting long enough to damage the liver permanently. To produce this condition requires much more than could be called a moderate use of alcohol, and it can be understood how by alternating the two primary factors involved, alcoholic intake and diet, the process may be accelerated or retarded indefinitely. This phase forms the classic cirrhosis of the portal type. Fat disappears from the liver when the body fat is exhausted, and the liver becomes smaller after prolonged starvation, fat rapidly disappears when the consumption of alcohol is discontinued, and the resumption of a normal diet or the administration of dextrose solution causes a rapid disappearance of fat as the liver fills with glycogen. The presence or absence of fat, then, has little significance in this late stage.

Connor has concluded that it is very doubtful whether in any person on a balanced diet alcoholic cirrhosis will develop. A person eating three regular, balanced meals a day will probably not become a chronic alcoholic addict, in the sense that this term is used here, as long as this regularity continues. It has been demonstrated in both man and experimental animals that it is possible to maintain metabolic equilibrium within safe limits even when large amounts of alcohol are taken habitually.

Less direct evidence for the relation of alcohol and cirrhosis was presented by Rowntree,<sup>181</sup> showing the reduction in the number of cases of cirrhosis observed in the United States after the passage of the

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181 Rowntree, L. G. Considerations in Cirrhosis of the Liver, J. A. M. A. 89 1590 (Nov 5) 1927

National Prohibition Act Evans and Gray<sup>182</sup> have recently reported statistics indicating that the incidence of cases of cirrhosis at the Los Angeles County Hospital has tripled since the repeal of the prohibition act

The relation of fatty infiltration and alcoholism to the etiology of portal cirrhosis will not explain the genesis of all cases of cirrhosis Many cases are noted in which the action of these two factors can be excluded specifically Other specific causes of cirrhosis are known, but these studies have done much to clarify the old clinical impression that led to the use of the term "gin drinker's liver "

The emphasis on the importance of the associated diet likewise is significant The regenerative and recuperative powers of the hepatic parenchyma are well known Bollman has reported that he has not been able to produce cirrhosis in dogs by the administration of carbon tetrachloride to such an extent that ultimate symptomatic recovery was impossible when the administration of the drug was stopped The time is yet to come when the clinician can make the same statement

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182 Evans, N, and Gray, P A Laennec's Cirrhosis Report of Two Hundred and Seventeen Cases, J A M A **110** 1159 (April 9) 1938

## News and Comment

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**Industrial Health** — The twenty-fourth annual meeting of the American Association of Industrial Physicians and Surgeons with the American Conference on Occupational Diseases and Industrial Hygiene will be held at the Hotel Statler, Cleveland, June 5 to 8, 1939. A program of timely interest and importance will be presented by speakers of outstanding experience in all the medical and engineering problems involved in industrial health. Further information may be procured from A. G. Park, convention manager, 540 North Michigan Avenue, Chicago.

**American Heart Association, Inc.** — The fourteenth scientific sessions of the American Heart Association, Inc., will be held at the Hotel Jefferson, St. Louis, May 12 and 13, 1939. A general program is scheduled for the first day and a program for the study of the peripheral circulation on the second day.



## Book Reviews

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**The Primate Thalamus** By A Earl Walker, M D Price, \$3 Pp 321, with 96 illustrations The University of Chicago Monographs in Medicine, Chicago University of Chicago Press, 1938

In this monograph Walker presents a comprehensive account of the anatomy, connections and function of the primate thalamus. A short historical introduction is followed by a detailed discussion of the gross and the nuclear structure of the thalamus of the macaque monkey, as typical of that found in the higher primates. In successive chapters consideration is given to the afferent connections of the thalamus, its relation to the cerebral cortex, the distribution of the projection fibers from the thalamic nuclei and geniculate bodies to the various cortical areas and the anatomic, physiologic and clinical significance of the thalamus. The author's extensive experiments, on which the book is based, were carried out entirely on the macaque monkey. The work was done at the University of Chicago, the University of Iowa, Yale University and the Laboratory of Neuropathology, Wilhelmina Gasthuis, in Amsterdam. The enormous literature on the thalamus is well summarized and woven into an orderly presentation of the whole.

In his study of the afferent connections of the thalamus, Walker utilized the Marchi technic to trace the centripetal degeneration following section of the spinal cord, destruction of the nuclei of the dorsal columns and section of the brachium conjunctivum. The projections of the thalamic nuclei to the cerebral cortex were studied by examining the retrograde degenerations in the nuclei by the Nissl method after decortication operations of varying extent. The results of these numerous experiments cannot be indicated here. In general, the intensity of the thalamic projection to the different cortical areas was found not to be uniform. The prefrontal cortex receives afferent fibers in great number from the nucleus medialis dorsalis, the motor cortex from the nucleus lateralis ventralis (which is the thalamic termination of fibers from the brachium conjunctivum) and the striate area of the occipital cortex from the lateral geniculate body. Walker has added considerable new information regarding the projection of the medial geniculate body, which receives afferent fibers from the cochlear nuclei of both sides. This portion of the metathalamus, he found, projects in an orderly fashion to a cyto-architecturally unique "koniocortex," located in a small area on the superior surface of the first temporal convolution. The inferior portions of the temporal lobes, the greater part of the parietal lobules and the premotor areas receive only slight thalamic projections.

Three functionally distinct groups of nuclei may be recognized in the thalamus. The midline nuclei, constituting the first group, remain relatively constant throughout the mammalian scale and are present in primitive animals not possessing appendages. They appear to be concerned particularly with visceral sensibility. The second group—the nucleus ventralis posterior, the nucleus ventralis lateralis and the geniculate bodies—receive fibers from primary or secondary sensory neurons and project to the cerebral cortex. They develop phylogenetically with the elaboration of the limbs and with the appearance of the special senses of vision and audition. The third group—the nucleus lateralis posterior, the nucleus medialis dorsalis and the pulvinar—are of recent development, they do not receive afferent somatosensory fibers, but they do project to the cerebral cortex. They "appear to be related to the highest and most recently developed sensory modalities."

In this monograph Walker has summarized the present knowledge of the thalamus as the great substation which receives all sensory data from the environment and initiates their organization. In addition, he has contributed valuable

material from his own painstaking work and has furthered the knowledge in important respects. His book will aid the neurologist in understanding how the nervous system receives and organizes the sensory material out of which behavior is ultimately compounded. Although essentially a study in anatomy, this work will prove of interest and value to the neurophysiologist and to the clinician, who must understand the symptoms of neurologic disease. An extensive bibliography materially increases the usefulness of the book.

**Diagnostics urgents Abdomen** By H. Mondor. Third edition. Price, 210 francs. Pp 1,120, with 248 illustrations. Paris: Masson & Cie, 1937.

What could be called the leitmotiv of this commendable work is the subscript to one of the illustrations: "Appendix of a little girl, operated upon, *thanks to her doctor* [italics not in text], for a gangrenous appendicitis which had not yet perforated." It is for the general practitioner that this book was written. The physician who has the privilege of first viewing the drama of the "acute abdomen" is the chief object of the author's efforts. He emphasizes, rightly, that the physician who must attend the patient with an acute abdominal condition in his home, deprived of instant access to a laboratory and consultations, bears a great responsibility. The victim's life is on a balance, with time measured in hours on the other pan. The diagnosis and the decision for surgical intervention must be made rapidly. The signs and symptoms which indicate the proper course toward relief and recovery are few and must be diligently sought and as expertly interpreted. It seems to the reviewer that this book offers as excellent a guide for such a search and for interpretation as could be expected.

The method of presentation is not dryly didactic. No speculation on pathogenesis, no detailed description of lesions and no discussion of therapeutics or of surgical technics are included. The dozen or so intra-abdominal disorders which demand prompt surgical treatment if the victim is to survive are the scope of the book. Much less attention is given to the nonsurgical diseases which simulate the "acute abdomen." The text is pleasantly written and is often almost journalistic in its terse economy of words. The author, surgeon to the Hôpital Bichat, illustrates his points with many case histories from his practice and from the experience and works of his colleagues. These histories are, in general, appropriate and are related in a manner more reminiscent of the "ward walk" than of the professorial lecture. Because the book is intended to be read by general practitioners and to simulate a personal conference, there is no formal bibliography, but many quotations, statistics and aphorisms of other surgeons are included and acknowledged.

Careful reading of this book should be valuable to any physician or student not only for the factual material but also for the highly idealistic and utilitarian attitude toward the grave problem of the "acute abdomen."

**Heart Failure** By Arthur M. Fishberg, M.D., Associate in Medicine, Mount Sinai Hospital, New York. Cloth. Price, \$8.50. Pp 788, with 25 illustrations. Philadelphia: Lea & Febiger, 1937.

This book is rather unique in that it deals with heart disease only as it concerns heart failure. The various mechanisms leading to heart failure are discussed, as are also the circulatory changes that occur as a result of failure. In thus eliminating a discussion of heart disease other than that concerned with failure the author has been able to include a tremendous amount of information without making the book unduly large.

A consideration of the alterations of the circulation and the blood that are attendant on failure deals with blood volume, venous pressure, blood velocity, cardiac output and the other physiologic studies that have recently done much to help clear up the subject. Each of these subjects is generously dealt with, and the author has shown a nice discrimination in choosing those portions of the subjects that have a direct clinical application.

He then discusses the changes consequent on failure, such as dyspnea, edema, pulmonary engorgement and the like. This leads finally to a consideration of the heart itself, the mechanisms of failure and the accompanying dynamics of the circulation, always with a view to the clinical application of the material set forth.

There is an adequate discussion of the recent physiologic work that bears on the subject. The author gives his own views, together with the views of those with whom he is in agreement. In addition, he discusses current theories with which he disagrees and gives his reasons therefor.

Peripheral vascular failure, or shock, is definitely placed in its proper position as distinguished from heart failure.

While therapeutic measures are mentioned throughout the book as their rationale is developed—or as their use is contraindicated, treatment is again discussed in a separate section.

The author has shown his willingness to depart from old pathways when such departure has seemed justified. He offers a classification of heart failure which is helpful if not perfect. His attitude toward the importance of the coronary circulation in all forms of heart failure and his characterization of peripheral vascular failure are evidence of a flexibility of mind.

The student, the general practitioner or the cardiologist, if he seeks information relative to the failure of the circulation, will find it in this book.

**Zur Entdeckung der Insulinschocktherapie bei akuten Geisteskrankheiten, insbesondere bei der Schizophrenie.** By Dr Julius Schuster. Price, 2 pengo. Pp 90. Budapest: Druckerei der Pester Lloyd-Gesellschaft, 1938.

The author has apparently prepared this booklet to substantiate his claim for priority in discovering the usefulness of insulin in shock treatment of the psychoses. Priority, he says, is now falsely attributed to Sakel. By 1922 Schuster had arrived at the conclusion that mental disease could be favorably influenced by exceptionally large doses of insulin. The booklet includes brief abstracts of 30 case reports of various types of psychoses in which treatment with large doses of insulin was employed. The earliest of these records is dated January 1921 (Banting and Best announced the discovery of insulin in February 1922<sup>1</sup>).

Pages 15 to 65 are devoted to reviews of several phases of carbohydrate metabolism, and whenever possible these are discussed in relation to cerebral physiology. Schuster says that insulin acts in cases of psychoses by inducing "brain shock," which is related to protein shock and to the metabolism of protein, carbohydrate and fat.

Although the biochemical observations are interesting, the reader is not enlightened as to the mechanism by which hypoglycemia now "cures" psychoses.

**Heart Disease in General Practice.** By Paul D. White. In Fishbein, Morris. National Medical Monographs. Price, \$3. Pp 338, with 47 illustrations. New York: National Medical Book Co., Inc., 1937.

Using the method of questions and answers, Dr. White has produced a sort of catechism of heart disease. His wide experience in teaching and writing has made it possible for him to strip the subject of nonessentials, and the result is a really admirable summary of what one must know to deal intelligently with cardiac problems. It is hoped that the general physician will take advantage of this little book, only too often misled by the propaganda of the pharmaceutical houses, he uses all sorts of complicated preparations of dubious value when only a few simple drugs are really needed.

It is to be regretted that this excellent book is printed on such poor paper, even though the price is low.

## INJECTIONS OF HIGHLY CONCENTRATED LIVER EXTRACT IN TREATMENT OF IDIOPATHIC ULCERATIVE COLITIS

GARNETT CHENEY, M D

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Innumerable therapeutic agents have been advocated for the treatment of idiopathic ulcerative colitis. None of them has proved satisfactory, and few have proved of the slightest benefit. The oral administration of liver extract has been tried in the past, apparently with the usual lack of success.<sup>1</sup> It was not mentioned by Baigen or by those physicians discussing his most recent report on the therapy of ulcerative colitis,<sup>2</sup> nor was it mentioned in his report on the treatment of the anemia which commonly accompanies this disease.<sup>3</sup> Buie<sup>4</sup> in his recent textbook on proctology did not mention the use of liver in the treatment of ulcerative colitis. As a new form of highly concentrated liver extract for parenteral use is now available, this has been tried in the treatment of 8 patients with colitis, 7 of whom presented classic examples of the ulcerative type of unknown cause. Gratifying results were obtained in every instance with possibly 1 exception.

### REPORT OF CASES

CASE 1—*Chronic ulcerative colitis, with marked emaciation, spindlike diarrhea and recurring iritis, recovery following liver therapy*

*History*—R F Y, aged 43 years, formerly an insurance broker, was seen at home on Oct 2, 1937, complaining of abdominal pains and trouble with his bowels. He had been in and out of army and veterans' hospitals for eleven years because of ulcerative colitis and iritis. Appendicostomy was performed in 1930, and for

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From the Department of Medicine, Stanford University Medical School

1 Mackie, T T. Ulcerative Colitis. The Factor of Deficiency States, J A M A **104** 175 (Jan 19) 1935

2 Bagen, J A. Medical Management of Chronic Ulcerative Colitis, Proc Roy Soc Med **30** 351, 1937

3 Garvin, R O, and Bagen, J A. The Hematologic Picture of Chronic Ulcerative Colitis. Its Relations to Prognosis and Treatment, Am J M Sc **193** 744, 1937

4 Buie, L A. Practical Proctology, Philadelphia, W B Saunders Company, 1938

four months the bowel was irrigated through the stoma, which subsequently closed completely. He felt improved for two years after that but gradually became bedridden, owing to loss of weight and strength. He had abdominal soreness and cramps alternating with periods of diarrhea. In late years the stools when loose were often bulky, foul and foamy. Severe iritis occurred once or twice a year, usually during the periods of constipation. Numerous examinations of stools all failed to show amebas. Repeated proctoscopic examinations revealed ulceration of the bowel. Early and recent roentgenograms of the intestines showed a narrowed, smooth colon from the splenic flexure to the rectum. Agglutination tests of the blood did not reveal dysentery bacilli. A histamine test revealed achlorhydria. Results of tests of the urine, blood counts and a Wassermann test of the blood were not remarkable. His disease ran a course of remissions and exacerbations, but no form of treatment proved of any real benefit.

*Examination*—When he was first seen he was emaciated and weighed only 106 pounds (48 Kg). The left eye was badly inflamed. The whole abdomen was tender to pressure, and the descending colon was palpable and tender. He was not having any bowel movements except after oil enemas. The stool was unformed and oily and contained large amounts of mucus, but no gross or occult blood was present.

*Treatment and Course*—Treatment was started at home. A high caloric diet was ordered, and liver therapy was given. He received one intramuscular injection of liver extract a week for the first month, alternating 5 cc of a nonconcentrated extract<sup>5</sup> with 1 cc of a highly concentrated extract<sup>6</sup>. Thereafter the dose of the nonconcentrated extract was reduced to 3 cc, and the interval between injections was lengthened to two weeks. After four months the dose of the concentrated extract was reduced to 0.5 cc. He received only one injection in March 1938, when the use of the nonconcentrated extract was discontinued. Five-tenths cubic centimeter of the concentrated extract was given regularly every two weeks thereafter. There was diarrhea during the first two weeks of therapy, from six to eight semiformed foul stools being passed daily. During the next two weeks an average of three to four stools was passed daily. During the next two weeks three to four stools were passed per day, they were better formed and were no longer foul smelling. He felt much stronger, was up and about a little and had much less abdominal discomfort. Since Jan 1, 1938, there has usually been only one well formed bowel movement daily, and he has been able to come to the office for treatments. He gained 12 pounds (5.4 Kg) during the first month of liver therapy. Since then his weight has risen from 118 to 127 pounds (53.5 to 57.6 Kg). The iritis improved rapidly, so that he was able to read by the end of October 1937, and all signs of inflammation disappeared shortly thereafter. He has had no recurrence of the iritis. Proctoscopic examination on May 18, 1938, revealed a normal-appearing intestinal wall except for an area of hemorrhage.

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5 The product used was campolon, prepared by the Winthrop Chemical Company. It is a brand of purified solution of liver U. S. P. and contains approximately 5 units of anti-pernicious-anemia principle per cubic centimeter. The preparation has not been accepted by the Council on Pharmacy and Chemistry of the American Medical Association.

6 The product used was reticulogen (parenteral liver extract with vitamin B<sub>12</sub>, Lilly). Each cubic centimeter, according to the manufacturer, contains not less than 20 units of the anti-pernicious-anemia principle and not less than 1,000 international units of vitamin B<sub>12</sub>. The preparation has not been accepted by the Council on Pharmacy and Chemistry of the American Medical Association.

the size of a dime. No ulcers were present. Roentgen examination after a barium sulfate enema on the same day showed a smooth outline of the colon in the region of the splenic flexure, but elsewhere the mucosal pattern appeared normal. The sedimentation rate of the blood was 11 mm in one hour, and the differential neutrophil count was normal.

His general condition has so improved during the past eight months that he is contemplating returning to his work, after eleven and one half years of invalidism.

*Comment*—The remarkable improvement in the patient's condition has occurred after years of gradual decline and could hardly have been irrespective of liver therapy.

*CASE 2—Severe ulcerative colitis of a year's duration in a young adult, excellent relief with liver therapy*

*History*—E. F., a 21 year old man, a saxophone player, suffered almost continuously from dysentery for one year, gradually lost almost 50 pounds (22.7 Kg.) in weight and had to cease work. He frequently had low grade fever. The stools were rarely formed and usually showed blood, pus and mucus. No amebas were present. Cultures of the stools failed to reveal dysentery bacilli or Barga's diplococcus. Agglutination tests of the blood gave a negative reaction for dysentery bacilli. Repeated proctoscopic examinations revealed ulceration and edema of the lower portion of the bowel and at one time suppurative lesions. Roentgenograms of the colon after a barium sulfate enema revealed that the sigmoid flexure and the lower descending portion were poorly haustrated, irritable and tender. The mucosal pattern suggested the presence of small ulcers. A histamine gastric test meal showed free acid. The blood count was normal (except for leukocytosis following sulfanilamide therapy), and the urine was normal. The Wassermann test of the blood gave a negative reaction. Treatment with prolonged rest in bed, a high caloric, high vitamin and low residual diet, yeast and cod liver oil, liver and iron by mouth, sulfanilamide by mouth, and injections of Barga's vaccine proved unavailing. He had a brief period of improvement after treatment with pyrexia from typhoid vaccine and 30 cc of nonconcentrated liver extract<sup>5</sup> while in the hospital for a week in August 1937. He required ½ to 1 ounce (15 to 30 cc) of camphorated tincture of opium daily to obtain some relief from abdominal cramps and diarrhea. He grew progressively weaker, and in November dysphagia, moderate stomatitis and edema of the ankles developed. Ileostomy was contemplated.

*Treatment and Course*—The patient was in bed constantly while at home and was barely able to make an occasional visit to the office. Largely on account of the stomatitis he was given an injection of concentrated liver extract<sup>6</sup> on Nov. 30, 1937. He was having an average of ten watery bowel movements a day with great tenesmus at this time and weighed only 110 pounds (50 Kg.). The temperature reached 100 or 101 F. daily. He received two more injections of liver extract during the next two weeks before he began to show marked improvement. Chart 1 correlates his progressive recovery, as shown by the gain in weight and the disappearance of dysentery, with the injections of concentrated liver extract from Nov. 30, 1937, to May 26, 1938. During the third and fourth weeks of treatment the dysphagia and stomatitis disappeared, his appetite increased enormously, the edema of the ankles was much improved, the stools became formed and free from blood and pus and contained only small flecks of mucus, tenesmus no longer occurred and he gained 15 pounds (6.8 Kg.) in weight.

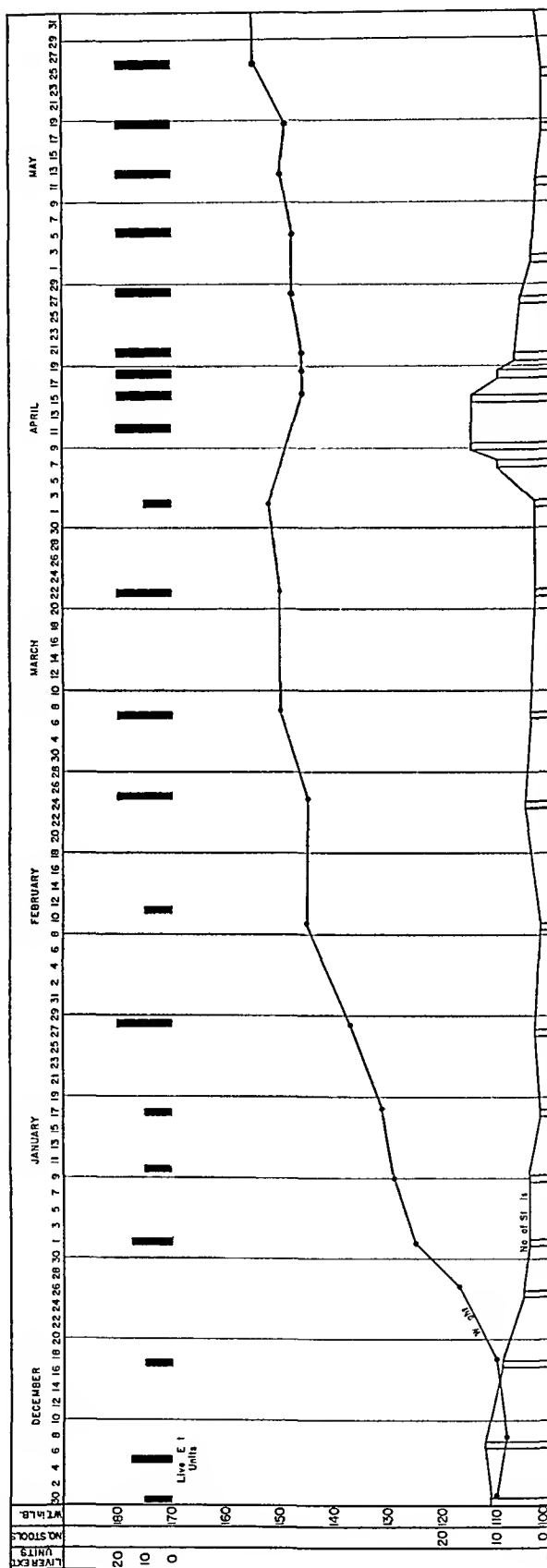


Chart 1 (case 2) —Correlation of parenteral liver therapy and clinical improvement in a case of severe chronic ulcerative colitis, as shown by cessation of diarrhea and gain in weight. A slight exacerbation of diarrhea late in February and a severe one in April followed reductions in the dose of liver extract.

During the next month, January 1938, he became active and was able to work two nights a week. He gained 12 pounds (5.4 Kg) more. During the middle of February he felt so well he worked late every night for a week. The dose of liver was reduced at the same time, and he failed to gain weight during the two subsequent weeks and showed an increase in the number of bowel movements, to four or five a day, with occasional tenesmus and a little discharge of mucus. The dose was increased, and the symptoms cleared up, although he had an average of three to five formed movements a day during March. Another examination after a barium enema on March 29, showed a condition similar to the one observed nine months previously, except that there was no tenderness or suggestion of ulceration. A proctoscopic examination on March 30 revealed normal-appearing mucosa in the lower portion of the bowel except for three small areas of localized hemorrhagic proctitis in the lower portion of the sigmoid flexure. No ulcers were present.

On April 4 he weighed 158 pounds (71.7 Kg), felt well and was working regularly. The dose of liver was again reduced, to 0.5 cc, within a few days he lost his appetite, and the diarrhea became severe, with ten to fifteen watery discharges. He lost 6 pounds (2.7 Kg, chart 1). Abdominal cramps were marked, and his temperature rose to 102 F on April 15. He received three injections of concentrated liver extract<sup>6</sup> (each of 1 cc) during the week from April 11 to 18. He was better by April 21, when he had another injection of 1 cc. During the following week the stools became formed, the cramps entirely disappeared, his appetite returned and he gained 4 pounds (1.8 Kg) in weight. He still had five or six stools daily. A week later he was as well as ever, and the number of stools was reduced to three a day. He remained well during May, receiving one dose of 1 cc of concentrated liver extract<sup>6</sup> every seven days. On May 31 the sedimentation rate was 7 mm in one hour, and the differential neutrophil count was normal.

*Comment*—The return to health and normal activity of this young man after a year of severe colitis paralleled the administration of large doses of liver. It is noteworthy that each of the two relapses shown in chart 1 followed a reduction in the amount of concentrated liver given.

*CASE 3—Hemorrhagic ulcerative colitis with anemia of two months' duration, rapid recovery with liver therapy*

*History*—A. L. S., aged 42 years, a laborer, was first seen in the hospital on Feb. 16, 1938, complaining of diarrhea and weakness. Ten years previously he was in an army hospital for an attack of diarrhea, which lasted nine weeks and cleared up completely. He was told that the illness was due to amebas. He had no further gastrointestinal disorder until seven weeks before admission to the hospital. Diarrhea gradually developed until he was having twelve to fifteen watery discharges daily containing blood and mucus. Abdominal pains were severe at the time of defecation. He had lost 25 pounds (11.3 Kg) in weight and had grown pale and so weak that he could not get out of bed. He had just completed a ten day course of treatment with emetine hydrochloride, without any improvement.

*Examination*—He was emaciated and sallow. His temperature was normal. The six stools examined failed to show any *Endamoeba histolytica*. No dysentery bacilli were found on culture of the stool, and agglutination tests for the bacilli gave a negative reaction. A blood count showed 55 per cent hemoglobin, 2,700,000 erythrocytes and 9,000 leukocytes, with a normal distribution. The urine was



normal Wassermann and Kahn tests of the blood gave negative reactions. Proctoscopic examination revealed a number of small ulcers with grayish bases in a dark red, velvety, edematous mucosa, which oozed blood readily. Roentgen examination of the bowel was unsatisfactory as the patient could not retain the barium enema.

*Course and Treatment*—The patient took nourishment poorly. Tincture of opium reduced the bowel movements to about eight daily, otherwise his wretched condition was unrelieved, and he continued to lose weight.

On February 23 treatment with concentrated liver extract<sup>6</sup> was started, the patient receiving 0.5 cc every other day intramuscularly. The relation of this treatment to the number and the type of stools passed and to his body weight is graphically shown in chart 2. A marked reduction in the diarrhea occurred within ten days, and he had less pain, but on March 2 severe renal colic developed on

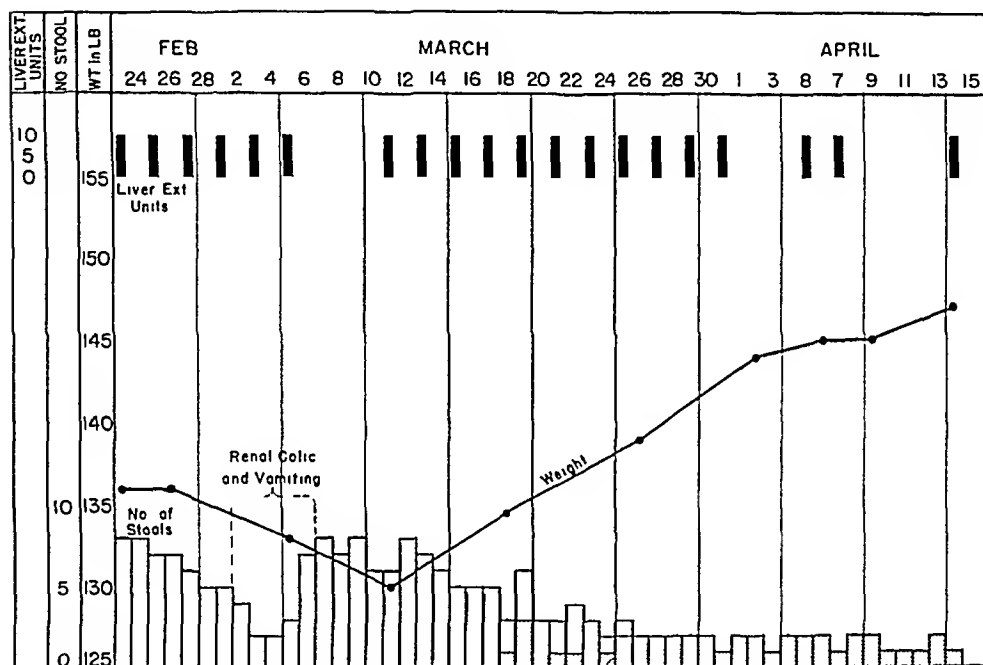


Chart 2 (case 3)—Showing a remission in a case of idiopathic ulcerative colitis coincident with injections of liver extract. A temporary increase in diarrhea was associated with renal colic. In charts 2 and 4 the unshaded columns indicate unformed stools, and the shaded ones indicate formed stools.

the right side, with vomiting for several days. Diarrhea and cramps reappeared and were as severe as previously. Regular opium and liver therapy was resumed on March 11. Within another week the diarrhea and pain had ceased, some of the stools were formed, no blood was discernible grossly in the feces and he was able to be up and about his room. Treatment with opium was stopped, without any increase in the bowel movements. One month after liver therapy was started he was having two normal movements daily, had gained greatly in strength and had increased 9 pounds (4.1 Kg) in weight in the past two weeks. By the middle of April, seven weeks after the start of the injections of concentrated liver extract, he was ready to leave the hospital. He was feeling well, and his weight had increased from 130 to 147 pounds (59 to 66.7 Kg),

a total gain of 17 pounds (7.7 Kg) in five weeks. Proctoscopic examination before dismissal showed a normal-appearing intestinal wall, without a trace of edema or ulceration. The blood count was normal. Roentgen examination after a barium enema showed absence of haustration in the distal portion of the colon.

*Comment*—The development of a complete remission in this case paralleled the liver therapy.

*CASE 4—Chronic ulcerative colitis, with a short remission subsequent to liver therapy*

*History*—The data concerning this patient were made available by Dr. De Witt K. Burnham. Miss V. B., aged 23 years, a saleswoman, entered the hospital on Feb. 22, 1938, complaining of "ulcerative colitis." She had Vincent's stomatitis two years before entry but otherwise had been well. Eight months before entry dysentery developed, and about twenty watery bowel movements occurred daily. The stools contained blood, pus and mucus. She had been confined to bed on an off since then and had not been up at all during the last two months. Severe cramps preceded the passage of stools. No loss of weight had occurred, but her usual weight was only 98 pounds (44.5 Kg). She had been markedly anemic, but this condition had cleared up. Examination of the stools did not show parasites, and culture gave negative results for dysentery bacilli. The diagnosis of ulcerative colitis was substantiated by a gastrointestinal roentgen study. Treatment with diet, opium and vitamins had failed to improve her condition materially, although there had been as few as seven stools daily on occasion. At entry she was having from four to nine evacuations daily and felt fairly well.

*Examination*—Physical examination revealed nothing remarkable. She was afebrile except for an occasional rise of temperature to 99.4 F. The urine was normal. A blood count was normal except for a leukocyte count of 15,200. Two liquid stools did not show amebas but contained much occult blood. Mucus and pus were not noted. Culture of the stools gave negative results for dysentery bacilli. Hinton and Kahn tests of the blood gave negative reactions. A fractional gastric analysis revealed normal acidity. A tuberculin test gave a moderately positive reaction but had given a positive reaction three years previously. A Frei test gave a negative reaction. Proctoscopic examination showed granular ulceration of the whole intestinal mucosa. Smears made of material from the rectal wall showed no amebas. A roentgen study after a barium enema demonstrated that the entire colon was tender, irritable, spastic and "smoothed out." A fine irregularity of the transverse colon was interpreted as probably being due to ulceration.

*Treatment and Course*—In addition to her previous treatment she was given a cod liver oil concentrate, calcium gluconate, enemas of salt solution and a course of instillations of carbarsone and a preparation of colloidal kaolin<sup>7</sup> into the lower portion of the bowel. On March 11, two and one-half weeks after entry she was given daily injections of 0.5 cc of concentrated liver extract<sup>8</sup> for nine consecutive days. She was dismissed from the hospital on March 30, five weeks after entry and only two and one-half weeks after the start of liver extract therapy. She had no liver therapy during the last ten days in the hospital. The diarrhea was unaltered, although her general condition was said to be improved.

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<sup>7</sup> The preparation used was kaomagma (John Wyeth & Brother, Inc.). Each hundred cubic centimeters contains 20 Gm of colloidal kaolin and 90 Gm of aluminum hydroxide gel.

She reentered the hospital for one day on April 4, three and one-half weeks after the first entry. For two weeks she had usually had only three movements daily, and these were well formed and often free from mucus. The abdominal cramps were definitely less severe, and she felt well. Proctoscopic examination at this time showed essentially the same condition as previously except that some areas of the mucosa seemed improved, no new ulcer formation was evident. She returned home. Early in May it was reported that on some days she had only one bowel movement, which was normally formed, and that she was free from abdominal pains. Later in May she was apparently having a relapse as pain and diarrhea had returned. Treatment with vitamin C intravenously was started. No further liver therapy was given, as her remission was not ascribed to the injections of concentrated liver extract given during the middle of March.

*Comment*—The beneficial effect of liver therapy is difficult to evaluate in this case as it was given over such a short period. The remission, which became evident about the fourth week after the injections of liver extract were started, appeared at about the same time as in the other cases and may well have been due to the liver extract. The subsequent relapse without further injections of liver extract is in keeping with this assumption.<sup>7a</sup>

*CASE 5—Low grade ulcerative colitis of long standing, with the first sustained improvement with liver therapy*

*History*—The record of this case was made available by Dr. A. L. Bloomfield. Mr. H. C., a student aged 21 years, first came under observation on Sept. 27, 1937, complaining of diarrhea. He had been in good health until one year before entry, when diarrhea and abdominal pains developed. This condition had been almost constant since then. There had been an average of three to eight poorly formed movements daily which contained blood and mucus. He had maintained his body weight and strength. Proctoscopic examinations repeatedly disclosed ulcerations. The stools never contained amebas, although a positive agglutination reaction for Flexner serum was obtained from a culture of fecal bacteria. Roentgen examination after a barium enema revealed no abnormality. The urine was normal. The blood count showed slight anemia. Kahn and Kline tests for syphilis gave negative reactions. Gastric analysis revealed hyperacidity. He was treated with diet, retention enemas, kaolin, vitamins A, B, C and D, antidyentery serum and streptococcus vaccine. He was reported to have shown some improvement temporarily after serum therapy. When he was first seen by Dr. Bloomfield, results of physical examination were unimportant, although the descending colon was palpable. The urine and blood counts were normal. Two examinations showed blood and pus in addition to formed stools. No amebas were seen. Culture gave negative results for the dysentery group of organisms. Proctoscopic examination revealed the typical picture of superficial chronic ulcerative colitis. Scrapings from the ulcers showed no amebas. A roentgen study after a barium enema showed no evidence of disease of the colon. A course of sulfanilamide treatment given in January 1938 was without benefit. Another course of vaccine therapy was started in February. The diarrhea persisted. The patient kept a daily account of his bowel movements, which showed an average of "forty per week."

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<sup>7a</sup> Subsequently, while receiving liver extract consistently, this patient became free from symptoms.

*Treatment and Course*—On March 15, 1938, injections of concentrated liver extract<sup>6</sup> were started. He received 0.5 cc three times a week for the first three weeks and 1 cc three times a week thereafter. On April 6, three weeks later, the diarrhea was not materially altered, but proctoscopic examination showed less edema and ulceration of the intestinal mucosa and some normal-appearing areas. Another proctoscopic examination was performed on May 13, five weeks later and just two months after the start of liver treatment. The intestinal wall was almost free from ulceration and edema but still bled easily if traumatized. The diarrhea had definitely improved during the past three weeks, the number of stools per week being twenty-seven, twenty and twenty-seven, respectively. On some days there had been only two or three movements. Gross blood had disappeared, and the amount of mucus was considerably diminished.

*Comment*—This patient seemed definitely improved clinically and by proctoscopic examination for the first time in one and one-half years. The improvement was coincident with liver therapy and took place after many other forms of treatment had been tried without benefit.<sup>7b</sup>

*CASE 6—Long-standing diarrhea, with the recent development of severe ulcerative colitis, two remissions occurring while liver therapy was in progress*

*History*—Mrs. R. A. C., aged 35 years, was seen in consultation with Dr. Ralph Howe on April 5, 1938. He had first seen her the previous November, when she complained of lassitude and diarrhea, and had cared for her since then. Since childhood she had suffered from digestive upsets and occasional looseness of the bowels and had never been robust or strong. She attended the Mayo Clinic fifteen years ago because of these complaints and was told she had mild colitis. One and one-half years ago, while in Pasadena, Calif., she was told that she had amebiasis and was treated with an amebicide (iodoxyquinoline sulfonate). She was not relieved but subsequently had some injections of liver extract and felt much improved. During the first two months under Dr. Howe's care she was hospitalized because of nausea, occasional vomiting, weakness, abdominal cramps, low grade fever and dysentery. The stools were frequent and watery and showed much pus and blood. Amebas were not found in repeated examinations. Culture of the stool and agglutination tests gave negative results for dysentery bacilli. Proctoscopic examination revealed a number of necrotic ulcers of the rectosigmoid region.

Many forms of therapy were tried, including continuous treatment with whole liver extract with iron and vitamin B<sub>1</sub> by mouth and ten injections of ascorbic acid intravenously. Because of her prostration and the development of anemia a blood transfusion was given on Jan. 15, 1938, and the next day treatment with 0.5 cc of concentrated liver extract<sup>6</sup> was started. Two subsequent injections of this liver extract were given at weekly intervals and another transfusion. Coincident with this liver therapy she improved markedly, the abdominal pains and dysentery ceased, her strength returned and she left the hospital the first of February. During the next six weeks she was in the best of health, "the best in years," and gained 20 pounds (9.1 Kg.) in weight. A proctoscopic examination the middle of March showed only two ulcers, both of which appeared to be healing. During the last part of March all her old symptoms returned,

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<sup>7b</sup> This patient recovered completely after milk was removed from the diet, and he no longer required liver therapy.

the diarrhea became profuse and the stools contained pus and blood. She reentered the hospital on April 12, suffering from great weakness, nausea, abdominal cramps, dysentery and fever.

*Treatment and Course*—She remained in the hospital and received 0.5 cc of concentrated liver extract<sup>6</sup> three times a week. By the third week she was much improved (chart 3). The diarrhea had practically ceased, the stools were formed and the amount of blood and mucus were greatly diminished. The temperature became normal, and her appetite was good. She returned home on April 27 and received three injections of the concentrated liver extract for the first week and had two injections a week regularly after that. She gained steadily in weight and strength during May, and there was an average of only two stools daily. Only slight traces of blood and mucus occurred during this time. When visited

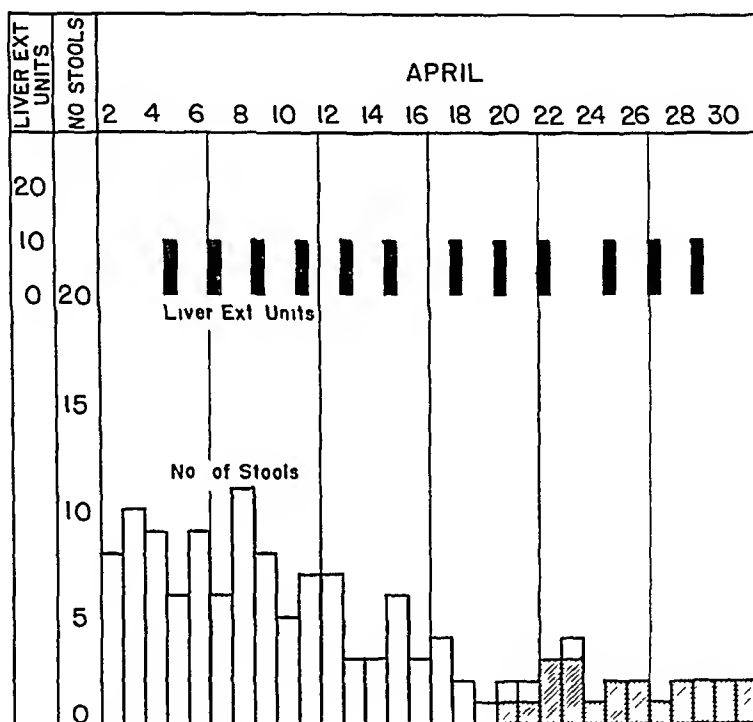


Chart 3 (case 6)—A rapid remission in a case of ulcerative colitis of the septic type, occurring coincident with the parenteral administration of liver extract. The patient had had a similar remission with liver therapy previously but subsequently had a relapse after the treatment was stopped.

at her home on May 23 she appeared well and made no complaint of any intestinal disorder.

*Comment*—Excellent remissions occurred twice in this case after the use of liver extract. As no other special therapy was instigated the second time, improvement could hardly be considered independent of injections of liver extract.

*CASE 7*—Extensive ulcerative colitis, with anemia, fever and marked emaciation, progressive for the last year and a half, an excellent remission being coincident with liver therapy.

*History*—Miss E C, a 20 year old student, was first seen in the hospital on Nov 4, 1937 She complained of diarrhea She had a brief attack two years before entry One year before entry the diarrhea returned, and she had suffered ever since from anorexia, recurrent vomiting, abdominal pains, fever, prostration and amenorrhea She had eight to fifteen stools daily, which were not formed and contained blood, pus and mucus She had lost 15 pounds (6.8 Kg) in weight recently and weighed only 87 pounds (39.5 Kg) at the time of entry Many forms of treatment had been tried, but none had helped her

*Examination*—She was thin and pale The descending colon was readily palpable as a cordlike structure Four examinations of stools failed to show any amebas All showed blood and pus Culture of stool showed *Streptococcus viridans*, *Bacillus proteus* and *Bacillus coli* but no dysentery bacilli Agglutination tests for typhoid, paratyphoid A and B and *Bacillus dysenteriae* gave negative results The urine was normal A Wassermann test of the blood gave a negative reaction Repeated blood counts showed hypochromic anemia, with the hemoglobin value varying between 50 and 60 per cent No leukocytosis occurred despite a slight rise in temperature daily Two Frei tests with different antigens gave negative results Proctoscopic examinations revealed an annular constriction about 5 cm above the anus The intestinal wall contained chronic and recent ulcers and scar tissue Smears from the ulcers did not show amebas A biopsy of the constricting lesion showed subacute suppurative proctitis Roentgen examination after a barium enema showed narrowing of the colon from rectum to cecum and absence of haustral markings in this area Five irregularities were noted on the surface of the bowel

Treatment included the employment of a high caloric and high vitamin diet, brewers' yeast, thiamin, cod liver oil, insulin, iron, sulfanilamide, fever therapy (typhoid vaccine) and blood transfusion, without any benefit She returned to her home in the country after one month's hospitalization For four months she constantly suffered from weakness, abdominal pains and diarrhea of varying degree During January 1938 she had a number of colonic irrigations while under the care of a chiropractor After this treatment she was much worse, so that during February she was confined to bed and had as many as twenty bowel movements daily During March she was somewhat improved and was able to be up and about At this time she was taking "every kind of vitamin except E" by mouth She had not consulted a doctor in two months

*Cause and Treatment*—She was seen by me at the office of Dr J C Drake, near her home, on April 8 and was given 1 cc of concentrated liver extract<sup>6</sup> intramuscularly She was having an average of ten stools in twenty-four hours, nearly all at night They were unformed and usually contained some mucus and blood Abdominal distress was frequent Her weight was 92 pounds (41.7 Kg) During the next two weeks she received three injections a week and thereafter two injections of the concentrated liver extract until May, when she received one injection weekly The relation of this therapy to the number and the type of the bowel movements and to the body weight is shown graphically in chart 4 Definite improvement was evident by the end of the third week of liver treatment, by the fourth week the diarrhea was greatly reduced, some of the stools were formed and contained no blood, the appetite was good, abdominal pains were much diminished, she had gained in strength and her weight had increased 7 pounds (3.2 Kg)

Early in May she contracted a severe infection of the upper respiratory tract, with some increase in the intestinal symptoms Although this infection lasted about two weeks, her general condition continued to improve, so that by the end

of May she weighed 105 pounds (47.6 Kg) and felt like returning to business college. Also she had had two normal menstrual periods in the last two months, her first in one and one-half years.

*Comment*—This girl was prostrated by ulcerative colitis, which was present in a severe and complicated form. Although she has not completely recovered during the seven weeks of intensive parenteral therapy with liver extract, her improvement has been so marked that a causal relation between it and the treatment can hardly be doubted.<sup>7c</sup>

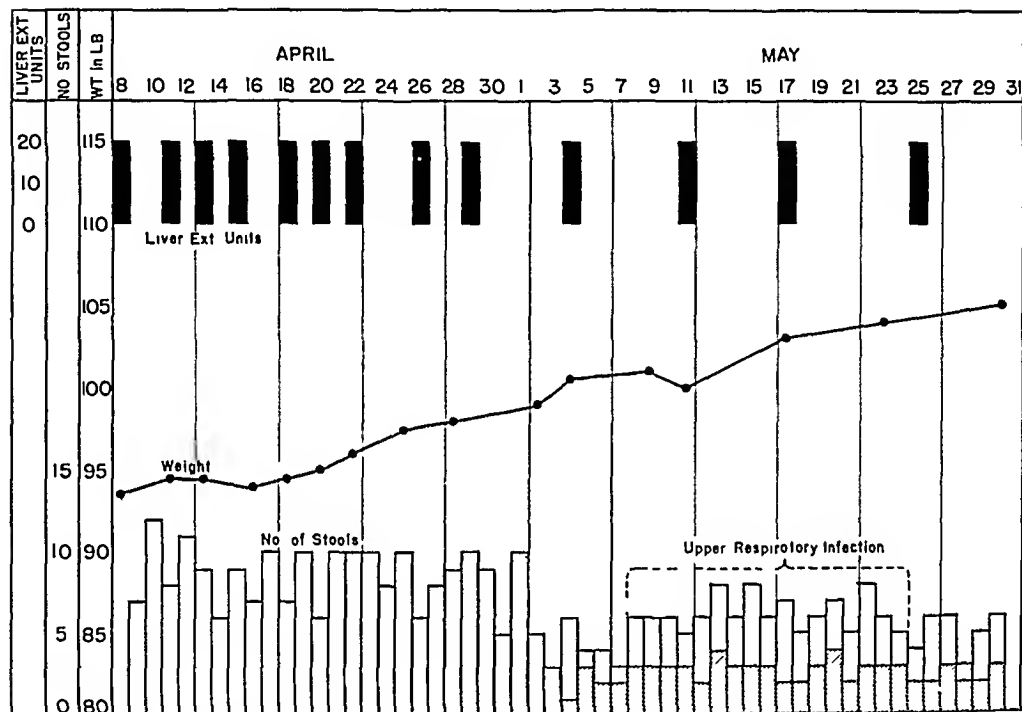


Chart 4 (case 7) —Showing the reduction of diarrhea and the gain in weight in a case of severe ulcerative colitis of over two years' duration. Improvement was coincident with parenteral liver therapy. A slight increase in diarrhea occurred during an infection of the upper respiratory tract. The patient is still under treatment.

*CASE 8—Chronic diarrhea with recurrent attacks of colitis, ulceration not proved, improvement with liver therapy*

*History*—Mrs P. S., a secretary aged 23 years, was first examined on June 15, 1937, when she had no complaints. Her appendix had been removed ten years previously. There had been some soreness in the region of the operative scar ever since. During the last two years she had suffered three attacks of severe abdominal pains and tenesmus, said to be due to an ovarian disorder. For the past year there had been two to four bowel movements daily. The stools were often soft and occasionally were accompanied by mucus. She had not lost weight.

<sup>7c</sup> With continued liver therapy she became free from symptoms and returned to school.

Physical examination revealed no abnormality except moderate tenderness in the left lumbar region and the right side of the abdomen. Pelvic examination revealed no abnormality. The urine was normal. The hemoglobin value was 74 per cent. The blood sedimentation rate was 8 mm in sixty minutes. A Kahn test of the blood gave a negative reaction. Pyelograms outlined a normal-appearing urinary tract.

She had had continuous intestinal disorder since Nov. 1, 1937, except for a respite during February 1938. She complained of recurrent abdominal cramps with soreness, distention, tenesmus, loose stools, that were poorly formed and often contained much mucus, and loss of strength. At times the lower portion of the abdomen was acutely tender. A low grade fever was present intermittently. Examination of the stool showed no ova or parasites. Roentgenograms of the gastrointestinal tract showed an irritable condition of the duodenal bulb, a tender, movable cecum that was normally outlined and a spastic area in the descending colon, suggesting the presence of ulcers. The sigmoid flexure was tender. There was no evidence roentgenologically of ileitis. In March she had to stop work because the symptoms had become so pronounced. At this time the blood count and sedimentation rate were normal. A tuberculin test (1:25,000) gave a negative reaction. Proctoscopic examination revealed no evidence of inflammation or ulceration in the lower 15 cm. of bowel. She was put to bed at home.

*Treatment and Course*—She was given a high caloric and nonresidual diet, a hemicellulose preparation<sup>8</sup> and capsules containing vitamins B<sub>1</sub> and B<sub>2</sub> complex,<sup>9</sup> and on March 8 she received her first injection of 0.5 cc. of concentrated liver extract<sup>6</sup>. These injections were repeated on March 10, 12, 14, 18, 22 and 29. She received three injections in April and two in May of 0.5 cc. each, except for a dose of 1 cc. on April 15. The third week after the injections of liver extract were started she began to improve, and by the fourth week she was free from abdominal cramps and tenesmus and for the first time in almost two years was having only one well formed stool daily. All therapy except the use of liver extract was stopped. She was able to return to work the latter part of April and has been free from symptoms since, except for some gas and slight soreness in the region of the cecum. On May 7 an alcohol test meal showed normal gastric acidity.

*Comment*—The findings in this case were typical of idiopathic ulcerative colitis in the stage before ulceration becomes pronounced. A remission took place during parenteral therapy with liver extract and has been maintained for two months.

#### COMMENT

The histories of these 8 patients with idiopathic ulcerative colitis show that a remission took place in each case about the same interval after treatment with injections of liver extract was started. Although remissions naturally occur during the course of the disease and the num-

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<sup>8</sup> The preparation used was metamucil, obtained from *Plantago ovata*.

<sup>9</sup> The preparation used was betalin compound (Lilly). According to the manufacturer, each capsule contains "150 International units vitamin B<sub>1</sub> (10 mg. Thiamin Chloride) and 40 Sherman units vitamin B<sub>2</sub> (G) with other factors of vitamin B<sub>2</sub> Complex from Liver-Stomach Concentrate."



ber of patients treated is small, such a uniformity of results could hardly be entirely coincidental, particularly as these patients had never shown sustained improvement with any other form of therapy. Most of them showed some evidence of improvement by the third or fourth week of treatment, and definite improvement was invariably manifest by the second month. Those with many ulcers and but slight physical disability were slower in showing an alleviation of symptoms which could be positively recognized. Certain symptoms are worthy of special attention.

The diarrhea was as a rule definitely diminished by the end of the third week. Usually the number of bowel evacuations was at least halved. One patient (case 3) showed rapid improvement, diarrhea ceasing at the end of the first week of treatment, only to recur coincident with the development of renal colic. In case 5 the diarrhea was not profuse, and well over a month passed before a definite reduction in the number of stools could be noted. Tincture of opium and camphorated tincture of opium were helpful adjuncts in reducing the diarrhea but never in themselves completely controlled it. Nervousness, excitement, intercurrent infections and other factors disturbing to the patient produced temporary increases in bowel movements, particularly early in the course of therapy. This is nicely illustrated in cases 3 and 7 (charts 2 and 4). Diarrhea ceased altogether during the second month, except in case 6, the number of movements ranging between one and three daily. If adequate maintenance treatment with liver extract was not continued, recurrence of the diarrhea occurred from two to four weeks after it had been stopped. In cases 2, 4 and 6 such relapses developed.

If the patient was not having any formed stools, some of them became formed by the end of the first month of treatment with injections of liver extract. Liquid defecation ceased entirely during the second month (charts 2 to 4). Gross pus commonly disappeared from the stool within one or two weeks. Gross blood and mucus were more persistent but were absent or occurred only in traces by the end of the second month of adequate therapy. They tended to reappear promptly if the diarrhea increased. The cramps and tenesmus improved as the diarrhea subsided and usually disappeared with the cessation of the expulsion of liquid feces and gas. When fever was present and closely observed, it tended to subside within five to ten days. This was particularly noticeable in cases 2 and 6, in which the temperature reached 102 F before the liver therapy was started.

When the loss of weight was marked, improvement in nutrition and gain in weight were often striking. The curves in charts 1, 2 and 4 show this graphically. The gain was commonly apparent by the third week of liver therapy and commenced even before diarrhea ceased. In 3 cases

(cases 4, 5 and 8) the loss of weight was not a feature of the illness. Improvement in the general condition was highly gratifying but was what would be expected in any one recovering from a prolonged siege of dysentery. In half the cases the patient has already returned to his normal mode of living after a prolonged period of disability.

Direct objective evidence of improvement in the colitis is furnished by follow-up proctoscopic examinations in 6 of 7 cases in which ulceration was observed before liver therapy was started. In 1 case the intestinal mucosa appeared normal two months after therapy was started. In 2 cases (cases 1 and 2) the intestinal wall was normal except for one or two small hemorrhagic areas four and eight months, respectively, later. In the 3 remaining cases (cases 4, 5 and 6) ulcerations were still present six weeks later, but pronounced improvement was evident in 2 and slight but definite involvement in 1. The last-mentioned patient (case 4) had received no maintenance therapy after the original nine consecutive days of treatment. It may be concluded from these observations that healing of the intestinal wall may be evident as early as the second month and may become complete subsequently. Further follow-up proctoscopic examinations are of course necessary to clarify the rapidity and extent to which healing of the pathologic process may take place. As structural changes in the bowel vary so much from case to case, naturally the rate of healing will vary in proportion to their extent and chronicity. Follow-up roentgen studies have been carried out in only 2 instances, cases 1 and 2. No definite changes in the intestinal outline have occurred, but it could hardly be expected that alterations in the contour of the intestinal wall due to fibrosis would be likely.

The exact amount of liver extract which must be injected to induce a remission in idiopathic ulcerative colitis cannot yet be stated. In the 8 cases described, excessively large doses were given as a rule, simply in the hope of obtaining some degree of therapeutic success. If in case 2 the temporary improvement which occurred in August 1937 can be attributed to the liver extract which had been injected, the response occurred after the administration of approximately 30 units in one week. A similar amount apparently initiated the first remission in case 6. In both these cases and in case 4 only a brief course of liver therapy was given although each patient improved temporarily, a relapse subsequently took place. The other courses of treatment were practically continuous, ranging from the injection of 10 or more units weekly to the administration of 10 to 20 units three times a week in the first weeks. The correct maintenance dose is also difficult to calculate except by the method of trial and error. Judging from the record in case 2, it may need to be as much as 20 units every seven to fourteen days. In cases 1 and 8 apparently as little as 10 units was needed every two

weeks. As clinically and pathologically idiopathic ulcerative colitis varies greatly in its severity, it would not be surprising to find that the dose of a successful therapeutic agent would also have to be variable. Practically, a patient should receive not only enough of this agent to make him well but also enough thereafter to keep him free from symptoms. At present this will have to be determined for each patient.

The concentrated liver extract used was reticulogen<sup>6</sup> in all cases except for brief periods in cases 1 and 2. A nonconcentrated preparation of liver<sup>5</sup> was used in case 1 in alternate doses with the concentrated extract and in the first course of injections given in case 2. Another brand of concentrated liver extract (Lederle) was used on two occasions in the early treatment in case 2 last winter. The only known advantage of reticulogen over the other brands of liver extract is its great concentration, making possible the administration of a highly potent substance in small doses. It seems possible that the addition of vitamin B<sub>1</sub> to reticulogen is an important factor, as it had not been added to the two other liver preparations used, but they seemed to be effective as far as may be judged from the available data.

In the management of idiopathic ulcerative colitis a trial of parenteral liver therapy should consist of the intramuscular injection of 10 units of liver extract three times a week for the first month, then 20 units a week for the second month and a maintenance dose of 20 units every two weeks thereafter. In exceptional instances the maintenance dose may have to be increased to 20 units every seven to ten days (see case 2 and chart 1). It may also be reduced to 10 units once in two to four weeks if the disease is mild.

A study of these 8 cases of idiopathic ulcerative colitis in which injections of liver extract were given suggests that liver contains some substance which promotes healing of the disease process in the bowel. The nature of this apparently beneficial factor is unknown. Vitamin B<sub>1</sub> has been added to reticulogen in the proportion of 1,000 international units per cubic centimeter, and liver extract already contains some vitamin B<sub>1</sub>. It seems highly improbable that lack of this vitamin alone can cause ulcerative colitis, as in the vitamin B<sub>1</sub> deficiency beriberi ulceration of the bowel does not occur. The same argument seems to hold good for the antipellagra (P-P) factor of the vitamin B complex, which is contained in liver. Although diarrhea is common in pellagra, colonic ulcers do not commonly occur except in far advanced or terminal conditions. The factor potent against pernicious anemia (fraction G of Cohn) contained in liver could hardly play a primary role, as ulceration of the bowel is not a symptom of pernicious anemia. However, this type of anemia may occur as a complication of nonspecific ulcerative colitis.<sup>3</sup> No exact analysis of reticulogen is as yet available, but it seems

likely that liver contains some as yet unknown substance which promotes healing of the bowel together with restoration of normal function and relief of symptoms of a disease which has heretofore withstood all therapeutic efforts to alter its chronicity and often fatal outcome. It must be emphasized that the reported findings in no way suggest a cure for ulcerative colitis, but they do suggest that a remission may be induced and maintained by the regular administration of liver extract by intramuscular injection.

#### CONCLUSIONS

Definite remissions have occurred in 8 cases of idiopathic ulcerative colitis subsequent to the intramuscular injection of concentrated liver extract.

Relapses have developed after the administration of liver extract has been stopped and have cleared up when liver therapy has been resumed.

It is the clinical impression of the physicians who have observed 7 of these 8 patients that the remissions were caused by the treatment with liver extract and were not coincidental. The eighth patient was insufficiently studied.

The administration of liver extract parenterally can in no way be considered a cure for idiopathic ulcerative colitis.

It is probable that the substance contained in liver which seems to exert a beneficial effect on the course of ulcerative colitis is one at present unknown and is not identical with vitamin B<sub>1</sub> or B<sub>2</sub> or fraction G of Cohn.

# VENTRICULAR ASYNCHRONISM IN BUNDLE BRANCH BLOCK

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The symptoms arising from damage of the branches of the bundle of His have been studied for years by many investigators with the aim of ascertaining (*a*) if there exists a complete block (*b*) and if so which is the branch blocked. Most of the study has been devoted to the electrocardiographic changes, and though these changes are important for the diagnosis of bundle branch block, considerable difference of opinion has developed among investigators as to their value in determining the branch involved.

Studying this problem experimentally and clinically, we have been able to find graphic signs of the ventricular asynchronism which is the fatal consequence of bundle branch block. Marked asynchronism in the contraction of the ventricles indicates with certainty that bundle branch block exists. Furthermore, it enables one to determine definitely which ventricle contracts first.

## VENTRICULAR ASYNCHRONISM IN EXPERIMENTAL BUNDLE BRANCH BLOCK

Although slight asynchronism has been found normally by Katz,<sup>1</sup> the onset of contraction of the ventricles may be considered to be practically synchronous.

This synchronism is due to the speed with which the impulse spreads through the branches of the bundle of His, exciting the two ventricles at the same time. If experimentally one of the bundle branches is crushed, marked ventricular asynchronism results. This was investi-

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1 Katz, L. N. Asynchronism of the Right and Left Ventricular Contraction and the Independent Variations in Their Duration, *Am J Physiol* **72** 655, 1925.

gated by Eppinger and Rothberger,<sup>2</sup> who observed—in only one experiment for each bundle branch—that after the left branch was cut, the onset of the pulse wave of the pulmonary artery preceded the onset of the wave of the aortic pulse by 0.02 to 0.03 second and vice versa after section of the right branch.

After cutting the right branch of the bundle of His in dogs and by means of optical registration of the mechanical events of the ventricular activity, we<sup>3</sup> have been able to demonstrate the following points:

(a) Asynchronism in the onset of contraction of the two ventricles, the contraction of the left ventricle preceding that of the right by 0.04 second (figs 1 and 2)

(b) Asynchronism in the onset of the ejection of blood from the two ventricles, the aortic pulse preceding the pulmonary pulse by 0.01 to 0.04 second (fig 3)

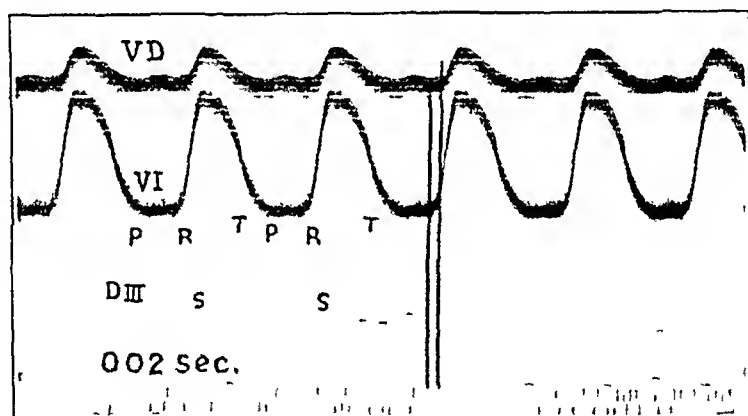


Fig 1—Synchronous records of right (VD) and of left (VI) intraventricular pressure (electrocardiogram, lead III, time, 0.02 second) for a dog after the right bundle branch had been cut. The rise of pressure in the left ventricle precedes that in the right by about 0.04 second.

(c) Asynchronism in the closure of the semilunar valves of the aorta and those of the pulmonary artery, the aortic second sound preceding the pulmonic second sound by about 0.06 second.

(d) Prolongation and, generally, reduplication of the first heart sound.

2 Eppinger, H., and Rothberger, C. J. Ueber die Sukzession der Kontraktion der beiden Herzkammern, insbesondere nach einseitiger Blockierung der Erregungsüberleitung, *Zentralbl f. Physiol.* 24: 1055, 1910.

3 Braun-Menendez, E., and Solari, L. A. Asincronismo ventricular por sección de las ramas del haz de His. I. Sección de la rama derecha, *Rev. Soc. argent. de biol.* 12: 331, 1936, abstracted, *Compt. rend. Soc. de biol.* 124: 251, 1937.

(e) Prolongation of the interval between the aortic incisura and the summit of the v wave of the venous pulse

After experimental section of the left branch we<sup>4</sup> also observed the ventricular asynchronism (in this case the contraction of the right

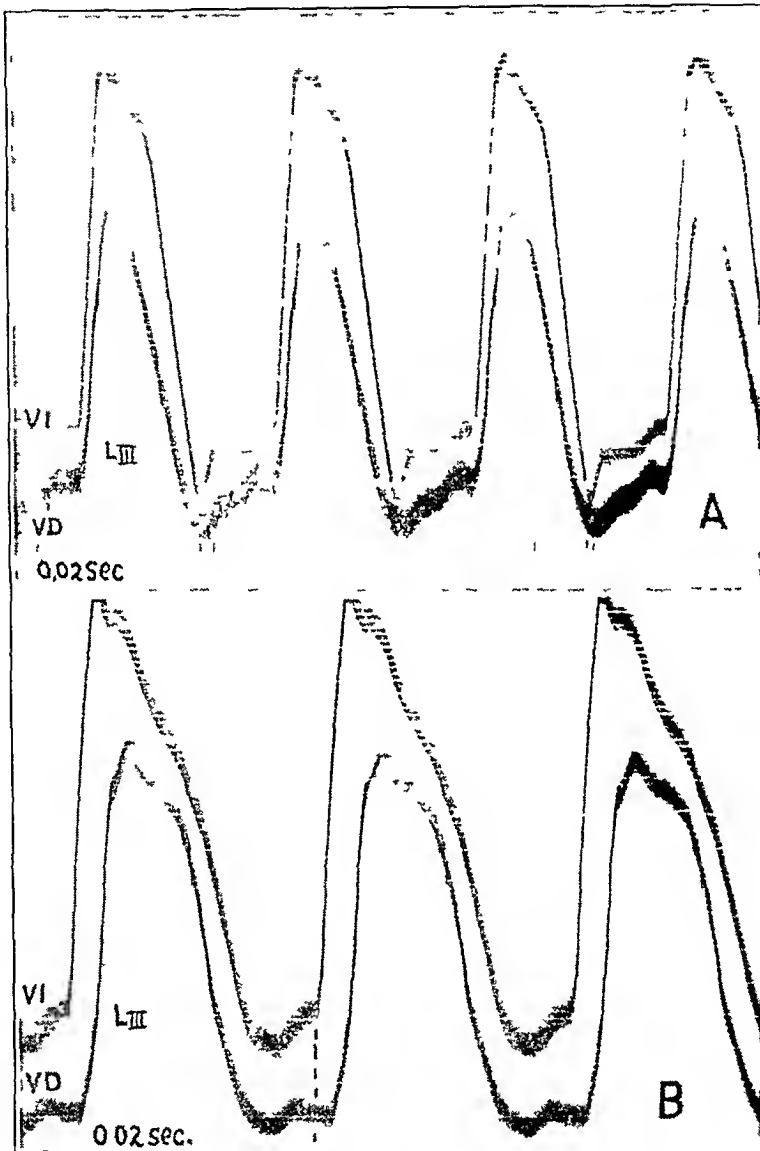


Fig 2—Synchronous records of the contraction in the left ventricle (VI) and in the right ventricle (VD), the cardiograms being made before (A) and after (B) the right bundle branch of the dog was cut (electrocardiogram, lead III, time, 0.02 second) Before section the ventricles contracted synchronously, after section the left ventricle contracted 0.04 second before the right

4 Braun-Menendez, E, and Solari, L. A. Asincronismo ventricular por seccion de las ramas del haz de His II Seccion de la rama izquierda, *Rev Soc argent de biol* **13** 33, 1937, abstracted, *Compt rend Soc de biol* **125** 531, 1937

ventricle preceded that of the left), although it was not so evident as in the case of section of the right branch

It is clear, then, that bundle branch block is followed by marked ventricular asynchronism, which no doubt in many ways influences the mechanical action of the heart

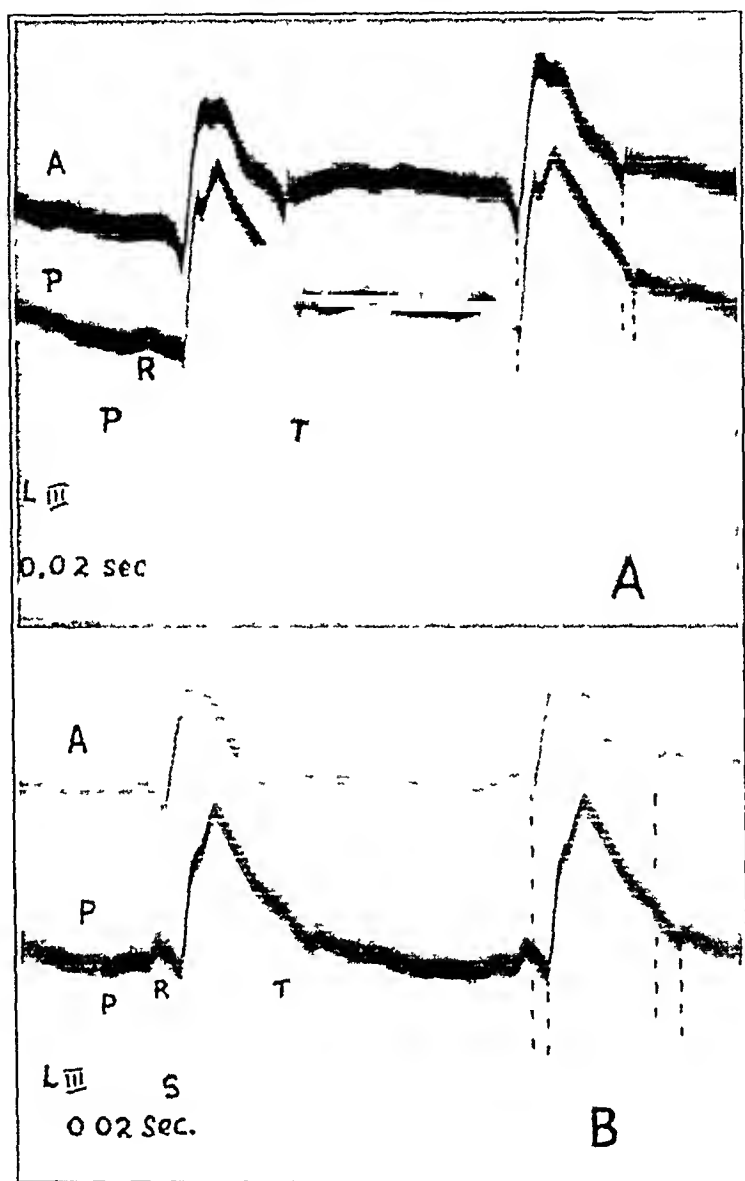


Fig 3—Simultaneous records of the aortic and of the pulmonary pulse before (A) and after (B) the right branch of the bundle of His of the dog was cut (electrocardiogram, lead III, time, 0.02 second) Before section the rise of the aortic and that of the pulmonary pulse were synchronous, and the aortic incisura preceded the pulmonary incisura by about 0.03 second After section of the right branch the rise of the aortic pulse preceded that of the pulmonary by 0.04 second, and the aortic incisura preceded the incisura of the pulmonary pulse by 0.06 second



## CLINICAL DEMONSTRATION OF VENTRICULAR ASYNCHRONISM

The electrocardiogram has heretofore been almost exclusively the only means employed for the diagnosis of bundle branch block. With this method Eppinger and Stoerk<sup>5</sup> diagnosed bundle branch block for the first time in man and determined which branch was involved. But after that the observation of many other clinical cases led authors to absolute disagreement. Some<sup>6</sup> observed (classic criterion) that when

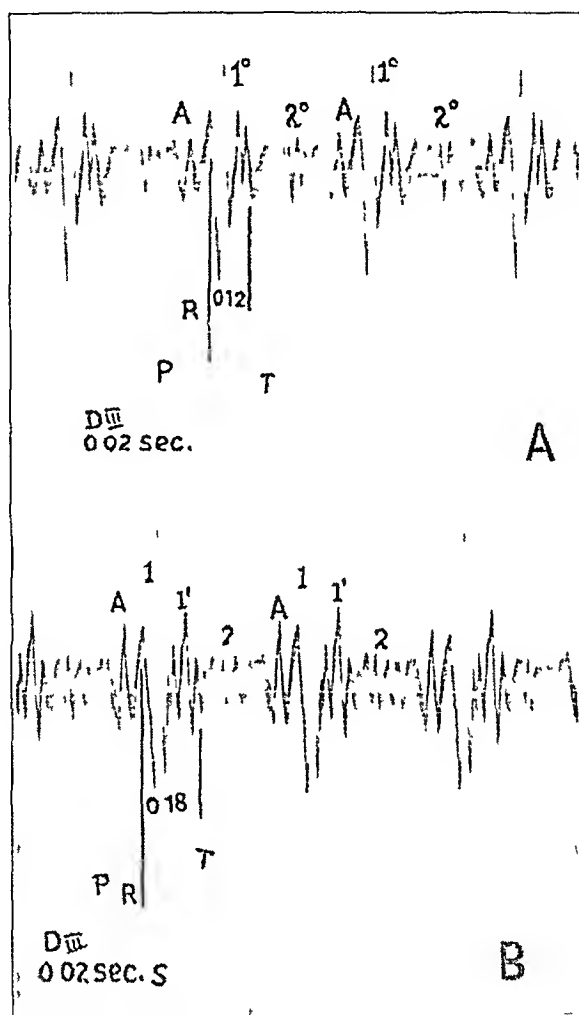


Fig 4—Heart sounds explored by way of the esophagus before and after section of the right branch of the bundle of His of the dog (electrocardiogram, lead III, time, 0.02 second). After section of the right branch the first heart sound was prolonged and reduplicated.

5 Eppinger, H., and Stoerk, O. Zur Klinik des Elektrokardiogramms, *Ztschr f klin Med* **71** 157, 1910.

6 Lewis, T. The Mechanism and Graphic Registration of the Heart Beat, ed 3, London, Shaw & Sons, 1925. Mahaim, I. Les maladies organiques du faisceau de His-Tawara, Paris, Masson & Cie, 1931. Rothberger, C. J. Zur Diagnose des Schenckelblockes, *Ztschr f klin Med* **123** 460, 1933.

the right bundle branch is blocked the electrocardiogram shows a tall, broad R wave in lead I and a deep S wave in lead III, the final T wave being in the reverse direction to the main initial wave in each lead. When left bundle branch block is present the electrocardiogram shows a deep S wave in lead I and a tall R wave in lead III.

In recent years some authors<sup>7</sup> have given convincing proof that the nomenclature of bundle branch block is the opposite of that just mentioned and that what has hitherto been called right bundle branch block is really left bundle branch block and vice versa.

Finally, according to Katz and his collaborators,<sup>8</sup> the electrocardiogram by itself is unable to give certain proof of the localization of bundle branch block.

In conclusion, although the electrocardiogram may give information as to the existence of bundle branch block, as Katz has pointed out "It would be unjustified to attempt to localize the site of bundle branch block from the direction of the major initial complex in the three leads of the electrocardiograms."

But there is a means of diagnosing bundle branch block with certainty and of localizing the site of injury, this is the verification of the

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7 Fahr, G. An Analysis of the Spread of the Excitation Wave in the Human Ventricle, *Arch Int Med* **25** 146 (Feb) 1920. Oppenheimer, B., and Pardee, H. The Site of the Cardiac Lesion in Two Instances of Intraventricular Heart Block, *Proc Soc Exper Biol & Med* **17** 177, 1920. Barker, P. S., Macleod, A. G., and Alexander, J. The Excitatory Process Observed in the Exposed Human Heart, *Am Heart J* **5** 720, 1930. Wilson, F. N., Macleod, A. G., and Barker, P. S. The Order of Ventricular Excitation in Human Bundle Branch Block, *ibid* **7** 305, 1931. Marvin, H. M., and Oughterson, A. W. The Form of Premature Beats Resulting from Direct Stimulation of the Human Ventricles, *ibid* **7** 471, 1932. Oppenheimer, E. T., and Oppenheimer B. S. Right and Left Bundle-Branch Block in the Human Heart, *Verhandl internat Kong Physiol* **14** 198, 1932, *Arch disc biol* **18** 277, 1933. Lundy, C. J., and Bacon, C. M. Premature Left Ventricular Beats from Electrical Stimulation of the Exposed Human Heart, *Arch Int Med* **52** 30 (July) 1933. Nichol, A. N. The Interpretation of Lead Inversion in Bundle-Branch Block, *Am Heart J* **9** 72, 1933. Wolferth, C. C., and Margolies, A. Asynchronism in Contraction of the Ventricles in the So-Called Common Type of Bundle-Branch Block. Its Bearing on the Determination of the Site of the Significant Lesion and on the Mechanism of Split First and Second Heart Sounds, *ibid* **10** 425, 1935. Brown, W. H. A Study of the Esophageal Lead in Clinical Electrocardiography. I. The Application of the Esophageal Lead to the Human Subject with Observations on the Ta-Wave, Extrasystoles and Bundle-Branch Block, *ibid* **12** 1, 1936.

8 (a) Katz, L. N., and Ackerman, W. Reversal in Direction of the QRS Complex of Experimental Right Bundle-Branch Block with Change in the Heart's Position, *Am Heart J* **8** 490, 1933. (b) Katz, L. N., Landt, H., and Bohning, A. The Delay in the Onset of the Left Ventricle in Bundle-Branch Block, *ibid* **10** 68, 1935.

ventricular asynchronism—its fatal consequence—by means of adequate registration of the mechanical cardiac events

#### COMMENT

If it were possible to determine directly in man the onset of contraction in the two ventricles, the verification of ventricular asynchronism would be easy. But as this is not yet possible, it was found necessary to record optically and simultaneously some of the mechanical events due to the activity of both ventricles.<sup>9</sup>

The optical tracings of the apex beat, the heart sounds, the central arterial pulse and the venous pulse in man when superimposed keep, under normal conditions, the time relations shown in figure 5

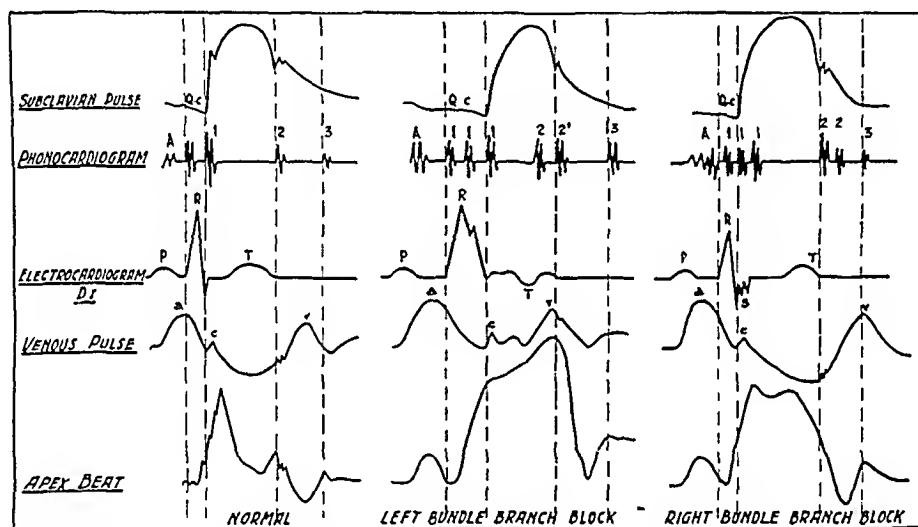


Fig 5—Superimposed curves for the subclavian pulse, heart sounds, electrocardiogram, venous pulse and apex beat to show the time relations of these tracings under normal conditions, with left bundle branch block and with right bundle branch block

As will be pointed out later, some of the events have especial significance. The first sound begins synchronously with the summit of the R wave in the electrocardiogram, and the second sound, which is due to the simultaneous closure of the aortic and of the pulmonary semilunar valves, begins synchronously with the bottom of the incisura of the

9 Battro, A. Braun-Menendez, E., and Orías, O. Asincronismo de la contracción ventricular en el bloqueo de rama, su demostración mediante el registro óptico de los fenómenos mecánicos de la actividad cardíaca. *Rev argent de cardiol* 3 325, 1936

central arterial pulse There is an interval between the rise of the R wave of the electrocardiogram and that of the central arterial pulse of 0.06 to 0.12 second

It must be pointed out that in the tracing for the venous pulse, which follows the right intra-auricular changes in pressure, the second sound is represented by a notch which interrupts the rise of the v wave, the summit of the v wave indicates the moment when the tricuspid valve opens, and the descending limb of the v wave indicates the phase of rapid inflow This phase is also represented in the curve of the apex beat (which follows the movements of the left ventricle) as a rapid early diastolic rise Because of the delay of the venous pulse waves in relation to those of the apex beat, the summit of this early diastolic rise is coincident with the last portion of the descending limb of the v wave, which is the moment when normally the third heart sound is recorded

As we<sup>3, 4</sup> have shown experimentally, two aspects may be considered in the ventricular asynchronism which follows section of one of the bundle branches (1) asynchronism of the onset of contraction of the two ventricles and (2) asynchronism of the end of systole in the two ventricles The verification of the existence of marked asynchronism of the onset of contraction or of the end of systole gives evidence of the existence of bundle branch block

The characteristic signs of ventricular asynchronism at the onset of systole that may be observed in man by optical recording of the mechanical events of cardiac activity are as follows

(a) The subdivision and prolongation of the first heart sound Castex,<sup>10</sup> King,<sup>11</sup> and King and McEachern<sup>12</sup> found by auscultation in many cases of bundle branch block a reduplication of the first sound that Wolferth and Margolies<sup>13</sup> recorded We<sup>9</sup> found that actually three groups of vibrations are to be distinguished (figs 6 to 8)

Under normal conditions the first heart sound is formed by two principal groups of vibrations, one of them corresponding to the

10 Castex, M Sur le dédoublement et le redoublement du premier bruit du coeur, *Arch d mal du coeur* **16** 401, 1923

11 King, J T The Clinical Recognition and Physical Signs of Bundle-Branch Block, *Am Heart J* **3** 505, 1928

12 King, J T, and McEachern, D The Nature of the Physical Signs of Bundle-Branch Block, *Am J M Sc* **183** 445, 1932

13 Wolferth, C C, and Margolies, A (a) The Various Types of Extra Heart Sounds, *M Clin North America* **14** 897, 1931, (b) Asynchronism in Contraction of the Ventricles in the So-Called Common Type of Bundle-Branch Block, Its Bearing on the Determination of the Side of the Significant Lesion and on the Mechanism of Split First and Second Heart Sounds, *Am Heart J* **10** 425, 1935

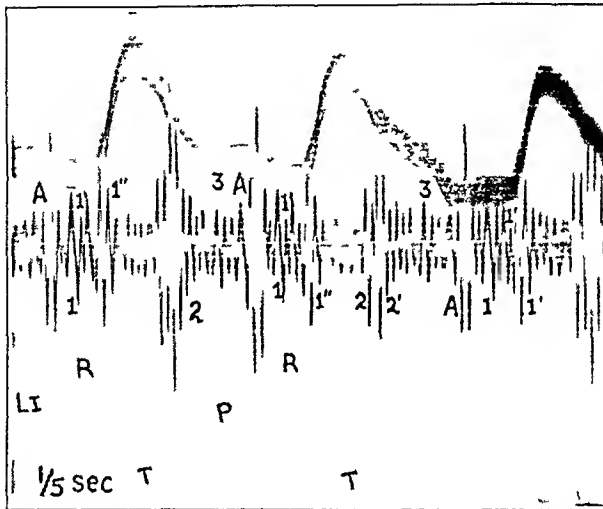


Fig 6—Optically recorded subclavian pulse, heart sounds and electrocardiogram (lead I) in a case of the so-called common type of bundle branch block (time, 0.2 second). The record of the heart sounds shows a loud auricular sound, a first sound composed of three groups of vibrations, a reduplicated second sound and a third heart sound. The interval between the rise of the R wave and that of the subclavian pulse is abnormally prolonged (Q-c, 0.16 second). This proved to be a case of left bundle branch block.

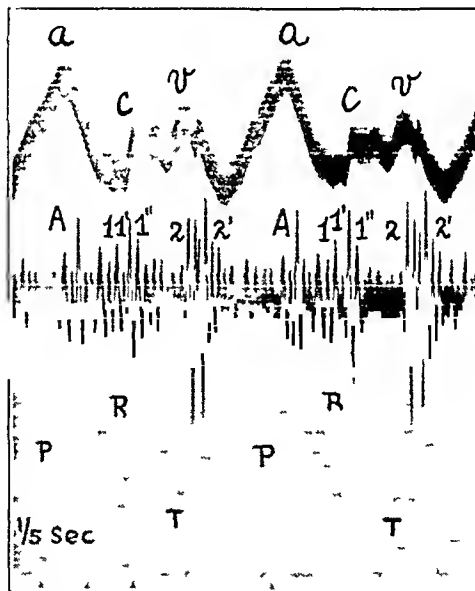


Fig 7—Simultaneous records of the venous pulse, heart sounds and electrocardiogram in a case of left bundle branch block. The phlebogram shows a typical change of contour. A notch synchronous with the second component of the reduplicated second sound is seen in the descending limb of the v wave.

isometric contraction phase and the other to the ejection phase. If ventricular asynchronism of more than 0.04 second is present, the second group of vibrations of the sound of one of the ventricles is added to the first group of the other ventricle, and there appear, consequently, three groups of vibrations. The three groups are not always clearly seen, as their demonstration depends on various other factors (e.g., area of registration and presence of postauricular vibrations).

(b) The other sign indicative of asynchronism at the onset of contraction of the two ventricles is the prolonged interval between the rise of the R wave and that of the central arterial pulse.<sup>14</sup> The value of this sign is relative, as it depends on many other factors. According to Katz, Landt and Bohning,<sup>8b</sup> an interval of less than 0.14 second discards the possibility of left bundle branch block, and an interval of

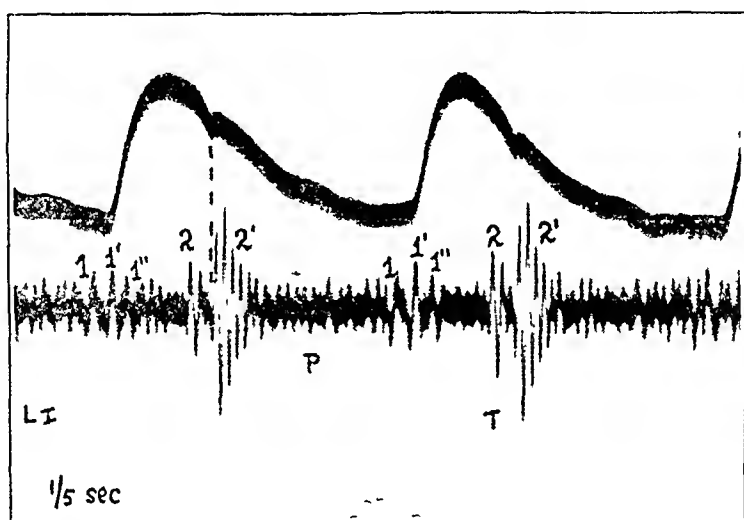


Fig 8—Optically recorded subclavian pulse, heart sounds and electrocardiogram (lead I) in a case of left bundle branch block. The second sound is reduplicated, and its first component precedes the incisura.

more than 0.18 second is probably good evidence of its presence (fig 9).

The most important signs for the diagnosis of bundle branch block are those indicating asynchronism of the end of systole or of the beginning of diastole. These may be obtained in man by the simultaneous record of the heart sounds and central arterial pulse and of the venous pulse and apex beat. These will be analyzed separately.

(a) Central arterial pulse and heart sounds. Under normal conditions the second sound is synchronous with the bottom of the incisura of the central arterial pulse or precedes it at most by 0.01 to 0.02 second. The incisura is due to the closure of the aortic semilunar valves, and

14 Nichol, A. N. The Interpretation of Lead Inversion in Bundle-Branch Block, *Am Heart J* 9:72, 1933. Wolfarth and Margolies.<sup>13b</sup> Katz, Landt and Bohning.<sup>8b</sup>

as these close more or less synchronously with the pulmonary valves, the second sound is single. When the two sets of semilunar valves close asynchronously (as in cases of experimental bundle branch block), the second sound may be reduplicated. By the simultaneous registration of this reduplicated second sound and of the central arterial pulse, sure information may be obtained as to which is the ventricle that first ends its contraction. If the second component of the reduplicated second sound coincides with the incisura of the central arterial pulse and if the first component begins more than 0.05 second before the end of the incisura (figs 9 and 10), the pulmonary valves close before the aortic valves, and it may be asserted that the ventricular asynchronism present is due to left bundle branch block.<sup>15</sup>

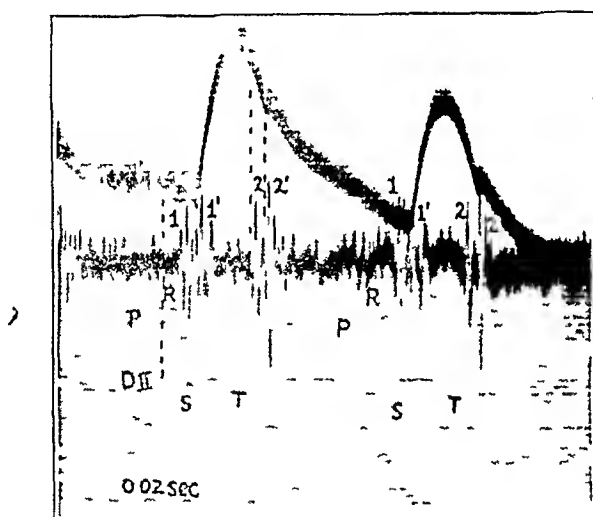


Fig 9—Optically recorded subclavian pulse, heart sounds and electrocardiogram (lead II) in a case of left bundle branch block. The second sound is reduplicated and its first component precedes the incisura.

(b) Curves for the venous pulse and for the apex beat. These curves give information as to the moment of the phase of rapid inflow in the two ventricles. The venous pulse follows the right ventricular events, and the curve for the apex beat represents the left ventricular events. The descending limb of the v wave of the venous pulse represents the phase of rapid inflow in the right ventricle, the early diastolic rise of the curve for the apex beat (or the third heart sound when present) represents the phase of rapid inflow in the left ventricle. Under normal conditions the end of the early diastolic rise of the portion of the curve for the apex beat and the third heart sound coincide with the last portion of the descending limb of the v wave. If this early

<sup>15</sup> Wolferth and Margolies<sup>13b</sup>; Battro, Braun-Menendez and Orias.<sup>9</sup>

diastolic rise anticipates and coincides with the summit of the v wave, it may be asserted that the onset of relaxation of the left ventricle has preceded that of the right, and therefore right bundle branch block is present (figs 11 and 12) On the other hand, when the end of the early diastolic rise of the curve for the apex beat (and the third heart sound) follows the end of the descending limb of the v wave of the venous pulse, it may be asserted that the ventricular asynchronism present is due to left bundle branch block (fig 13)

(c) In the curve for the venous pulse, apart from the time relations with the curve for the apex beat just mentioned, a significant change in contour of great importance for the establishment of the diagnosis of ventricular asynchronism, is to be observed (fig 14) In

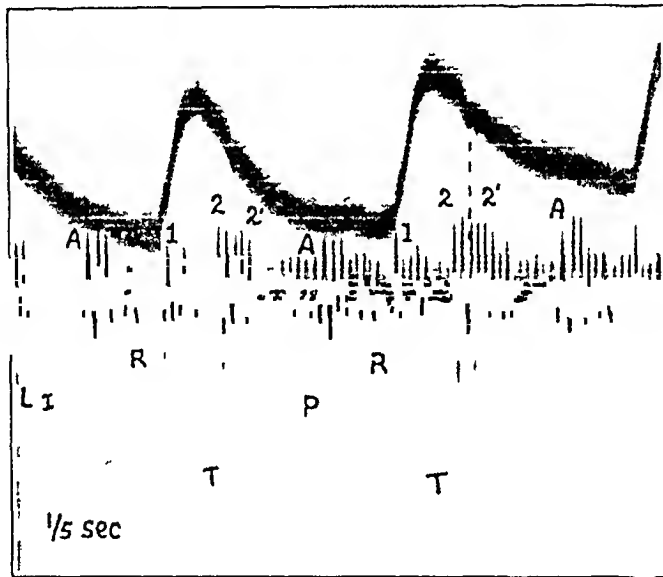


Fig 10—Optically recorded subclavian pulse, heart sounds and electrocardiogram (lead I) in a case of left bundle branch block The second sound is reduplicated, and its first component precedes the incisura

the curve for the optically recorded venous pulse the ascending limb of the v wave is interrupted by a small notch synchronous with the second heart sound, this is the second aortic sound, which is transmitted from the aorta to the jugular vein through the vena cava, or, in all probability, directly from the carotid or the subclavian artery to the jugular vein With left bundle branch block these vibrations are to be seen in the summit or early drop of the v wave, owing to the delay in the closure of the aortic semilunar valves (figs 7 and 13) On the contrary, when right bundle branch block is present and the left ventricle contracts before the right, the notch representing the vibrations of the aortic second sound is anticipated, and the interval between this notch and the summit of the v wave is prolonged (more than 0.13 second, maximal duration of the phase of normal isometric relaxation, figs 11 and 12)



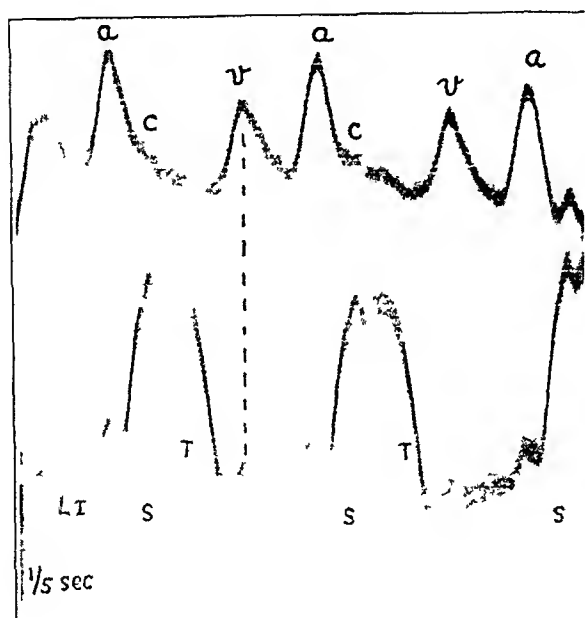


Fig 11—Simultaneously recorded venous pulse apex beat and electrocardiogram (lead I) in a case of right bundle branch block (time, 0.2 second). The early diastolic rise of the curve for the apex beat precedes the drop of the v wave of the phlebogram.

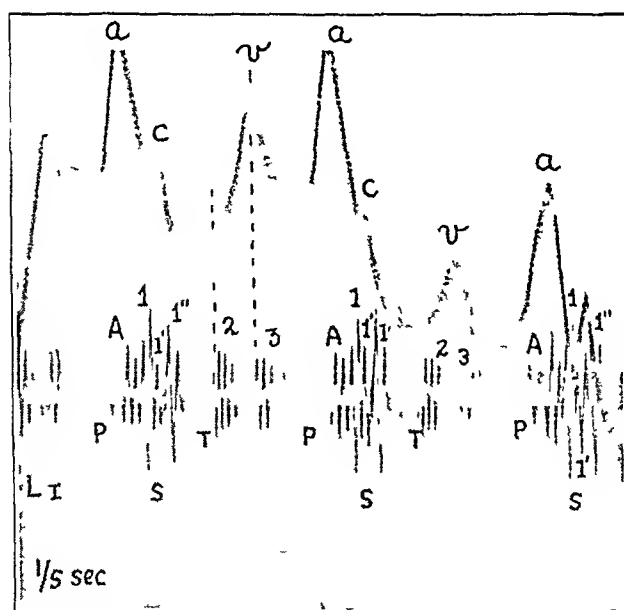


Fig 12—Simultaneously recorded venous pulse, heart sounds and electrocardiogram (lead I) in a case of right bundle branch block (time, 0.2 second). The interval between the notch in the curve for the venous pulse, which is synchronous with the second heart sound, and the summit of the v wave is prolonged. The third heard sound coincides with the summit of the v wave (as would be the case for the opening snap in a mitral stenosis).

These are the most important signs for the diagnosis of ventricular asynchronism. An auricular sound may be observed, and it has pathologic significance. When the heart rate is rapid a gallop rhythm may

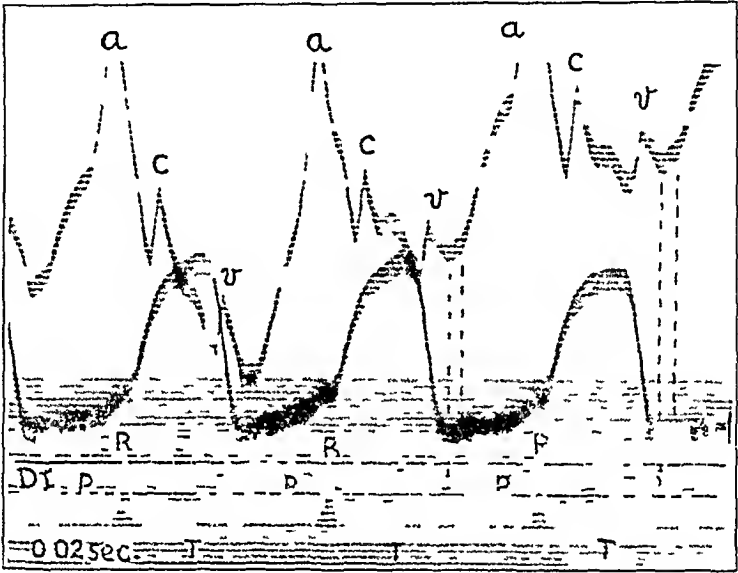


Fig. 13—Optically recorded venous pulse, apex beat and electrocardiogram (lead I) in a case of left bundle branch block, showing the change of contour of the phlebogram and its time relations with the curve for the apex beat. The descending limb of the v wave precedes the early diastolic rise of the curve for the apex beat (time, 0.02 second).

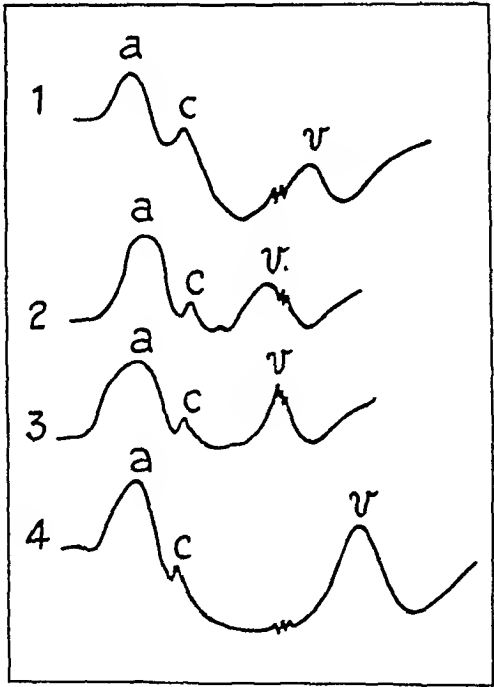


Fig. 14—The contour of the tracing for the venous pulse (1) under normal conditions, (2 and 3) with left bundle branch block and (4) with right bundle branch block.

ensue, if it is slow, the sequence of the auricular and the first heart sound may be interpreted by auscultation as showing a reduplicated first heart sound

We may briefly state that by optically recording for a patient the apex beat, the venous pulse, the heart sounds and the subclavian or

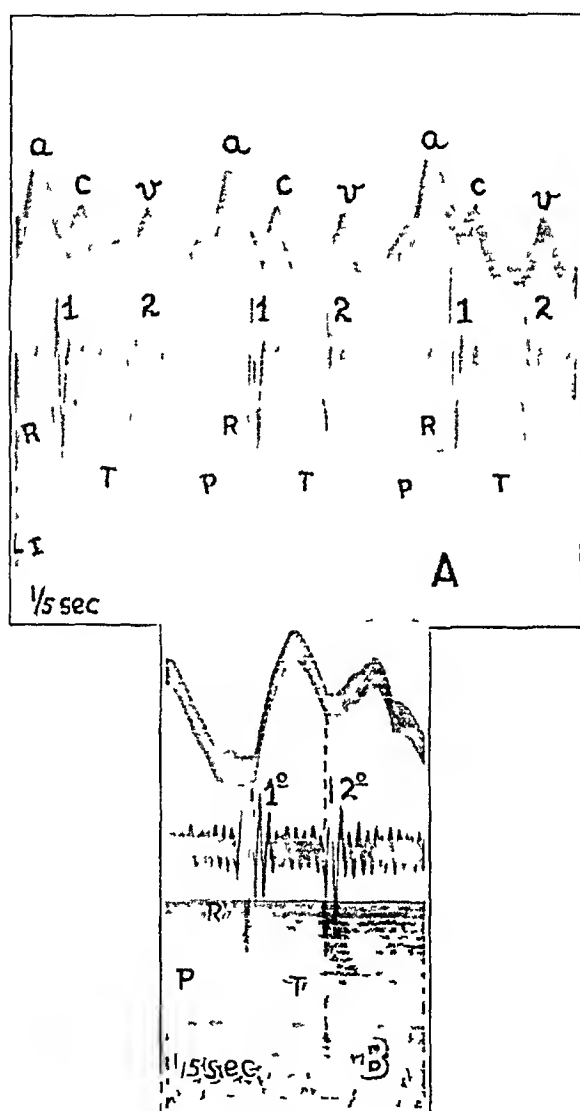


Fig 15—Optical records (A) of the venous pulse together with the heart sounds and (B) of the subclavian pulse together with the heart sounds, showing no sign of asynchronous action of the two ventricles in a case of so-called bundle branch block with a short PR interval (electrocardiogram, lead I, time 0.2 second)

carotid pulse simultaneously, it is possible to recognize (1) the existence of ventricular asynchronism and hence of bundle branch block, and (2) the localization of the bundle branch block by determining which ventricle contracts first

Applying these procedures, a study was made<sup>9</sup> of 20 patients whose electrocardiographic records were considered as characteristic of so-called bundle branch block. In 17 cases there were electrocardiographic records of the so-called common type of bundle branch block (right bundle branch block, according to the old nomenclature). In 15 of these cases

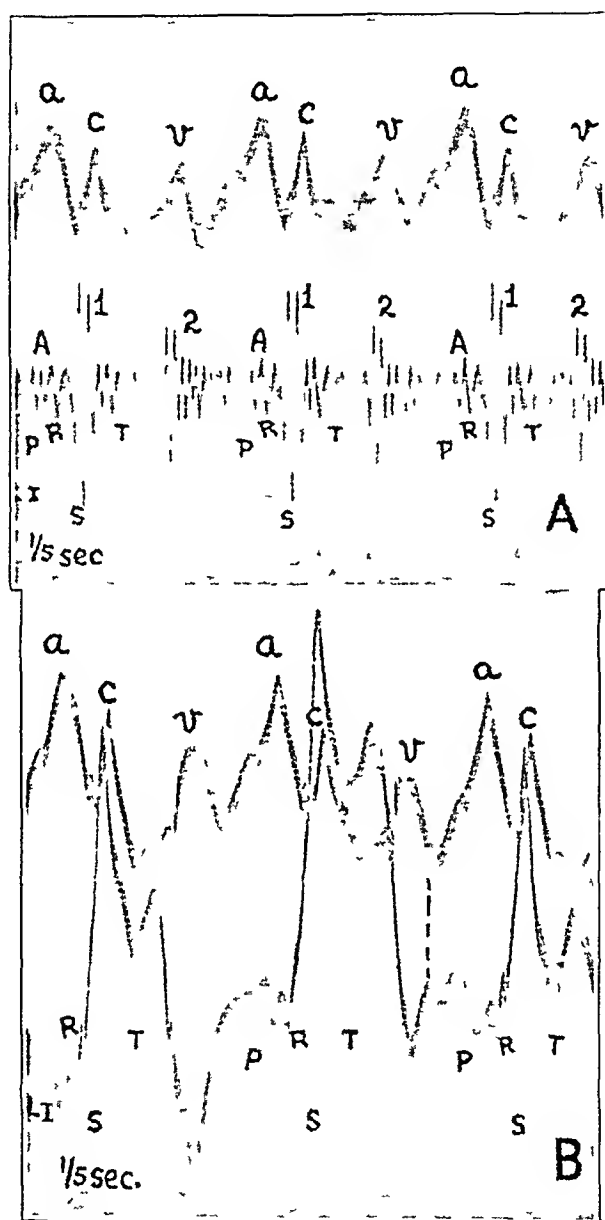


Fig 16—Optical records (A) of the venous pulse together with the heart sounds and (B) of the venous pulse together with the apex beat in a case in which the electrocardiogram was characterized by an abnormally long QRS interval and by broad S deflections in lead I. No signs of ventricular asynchronism were seen (time, 0.2 second)

there were obvious signs that the right ventricle contracted first, thereby really indicating left bundle branch block. In the other 2 cases no signs of asynchronism could be detected (fig 15)

Of the 3 cases in which the electrocardiographic records were characteristic, according to Wilson and his associates,<sup>16</sup> of right bundle branch, in 1 a clear precedence of the left ventricle was actually found, but in the remaining 2 cases all signs of asynchronism were lacking (fig 16)

From these observations the following conclusions may be drawn

1 When left bundle branch block is present the electrocardiogram shows a tall, broad S in lead III

2 Right bundle branch block may exist when the alterations described by Wilson and his associates<sup>16</sup> as characteristic of right bundle branch block are present

3 Electrocardiograms with the characteristic features of bundle branch block may not be accompanied by signs of ventricular asynchronism

This last assertion has considerable value, for we<sup>1</sup> have experimentally proved that whenever the section interrupts completely one of the bundle branches, marked ventricular asynchronism follows. On the other hand, whenever after section of a branch an electrocardiographic alteration appeared but no asynchronism could be detected, postmortem examination proved that the bundle branch had not been completely interrupted

#### SUMMARY AND CONCLUSIONS

Bundle branch block experimentally produced in dogs is followed by marked ventricular asynchronism, and it may be assumed that the same happens in human beings with bundle branch block

Optical recording of the apex beat, the venous pulse, the heart sounds and the central arterial pulse simultaneously makes it possible to recognize whether or not the ventricles beat synchronously or, in the absence of synchronism, which ventricle contracts first

Investigations carried out in this way have demonstrated that the electrocardiographic alterations which, according to the older view, were considered as characteristic of right bundle branch block are in fact encountered in cases of left bundle branch block

Electrocardiograms with all the characteristics of bundle branch block may exist without there being any detectable asynchronism and hence without there being complete block

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16 Wilson, F. N., and others. The Significance of Electrocardiograms Characterized by an Abnormally Long QRS Interval and by Broad S Deflections in Lead I, *Am Heart J* 9: 459, 1934

In conclusion, it may be advanced that the electrocardiogram which shows pronounced alterations affords good evidence of intraventricular block. However, it does not offer a reliable means for establishing a diagnosis of complete bundle branch block or, furthermore, for the localization of the branch involved. The adequate recording of the mechanical events due to cardiac action affords the only means for determining the existence of ventricular asynchronism, thereby allowing the recognition of delayed excitation through one of the bundle branches and the localization of the functional disturbance.

# NEUTROPHILIC LEUKOCYTOSIS IN SPINAL FLUID ASSOCIATED WITH CEREBRAL VASCULAR ACCIDENTS

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The present paper records 6 cases in which softening or hemorrhage within the brain was associated with the presence of polymorphonuclear neutrophilic leukocytes in the spinal fluid in such numbers as to suggest the diagnosis of meningitis or at least of some degree of meningeal irritation. We believe that this leukocytosis represents an aseptic reaction of the meninges to the damage within the brain. Except for the first, the cases are reported in slight detail for sake of brevity.

## REPORT OF CASES

CASE 1—L L, a Negress aged 49, was admitted to the medical service of the Baltimore City Hospitals on Sept 13, 1937, in a moribund state. The only history available was that the patient went to bed on Saturday night, September 11, in her usual state of health, which was excellent. Apparently she lost consciousness during the night and never regained it. There was no history of hypertension or any previous illness.

*Physical Examination*—The temperature was 100 F (rectal), the pulse rate 92 and the respiratory rate 28. The patient was a middle-aged Negress, well developed and nourished. She was in a state of coma, from which she could not be aroused. The respirations were of the Cheyne-Stokes type. There was moderate retraction of the head and marked rigidity of the neck. The eyes looked to the right and did not move beyond the midline. The right pupil was smaller than the left, and both reacted sluggishly to light. The fundi appeared normal except for some fulness of the veins. The lungs were clear on percussion and auscultation. The heart was not enlarged, and no murmurs were noted. The

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blood pressure was 155 systolic and 110 diastolic. The right arm and leg were moved spontaneously, and there was no spasticity. The left arm and leg were slightly spastic and were never noted to move at all. The reflexes were hyperactive on both sides, and there was bilateral plantar extension. Kernig's sign was present.

*Laboratory Data*—The urine had a specific gravity of 1.013 and gave a 3 plus reaction for albumin, microscopically only 7 to 8 white cells and a rare hyaline cast were noted. The blood count was as follows: red cells 4,260,000, hemoglobin 13.7 Gm, white cells 19,200, predominantly polymorphonuclear. The nonprotein nitrogen was 46 mg per hundred cubic centimeters. Lumbar puncture revealed a pressure of 175 mm of water, with a definitely positive Pandy reaction and a cell count of 2,000, of which 95 per cent were polymorphonuclears. No organisms were seen on smear, and none were grown on culture. Blood cultures were negative. The result of the Eagle precipitation test was negative, and the Wassermann reaction of the spinal fluid was anticomplementary. The colloidal mastic test gave the reaction of 5555555554.

*Clinical Course*—The case was considered as possibly one of meningitis or of ruptured abscess of the brain with leptomeningitis. Immediately after the lumbar puncture 30 cc of antimeningococcus serum was given intrathecally. Lumbar punctures were instituted twice a day and serum given. The cell counts on successive punctures were 3,700, 7,200, 16,000, 10,800, and 9,400, with 88 to 95 per cent polymorphonuclear cells. Some of the increase was naturally attributed to the administration of the serum. No red blood cells were found. Repeated smears and cultures of the spinal fluid revealed no organisms. On the second day after admission 300 cc of 0.8 per cent sulfanilamide was given subcutaneously, and this dose was repeated daily. The patient never regained consciousness. Her temperature gradually rose to 106 F, and she died on the fifth day after hospitalization.

*Gross Examination at Autopsy*—Scattered small patches of consolidation were seen in the lungs. Both ovaries were practically replaced by what were obviously dermoid cysts.

*Brain*—The convolutions of the brain were flat. The meningeal veins were filled with blood, but there were no hemorrhages in the leptomeninges. On coronal section at the level of the mamillary bodies a large excavation filled with dark, friable blood clot was observed. It occupied the region of the globus pallidus, putamen and external capsule on the right side and measured 2.5 cm across. It extended only 1 cm posterior to the mamillary body, where it ended as a small, soft, necrotic area in the white matter of the temporal lobe. Proceeding anteriorly from the mamillary body, the hemorrhage expanded into the white matter of the parietal region. The internal capsule, caudate nucleus and lateral ventricle were markedly pushed to the left. There was no evidence of escape of blood into the ventricle other than slight staining of its lining. The widest portion of the clot was situated at a point approximately 1 cm posterior to the tip of the temporal lobe. Here it measured 4 by 3.5 cm and extended to a point 12 mm from the temporal cortex. It almost completely replaced the island of Reil at this point, so that only a small rim of cortex remained. The hemorrhage became narrower as it passed into the frontal white matter, and 3.5 cm from the anterior pole of the frontal lobe it connected with another clot in the white matter. This smaller area likewise contained dark clotted blood and measured 2.5 by 1.5 cm at the level of the genu of the corpus callosum. The entire length of the larger



hemorrhage was 7 cm. The left hemisphere showed no gross pathologic changes. The larger cerebral arteries showed only a small amount of intimal sclerosis, while the smaller vessels were markedly affected.

*Microscopic Examination at Autopsy*—There was lobular pneumonia, scattered groups of alveoli containing moderate numbers of polymorphonuclear leukocytes and serum. Sections of the right ovary showed in the wall of the cyst a small mass of recognizable ovarian tissue. Nearby the wall enclosed a small mass of cartilage, atrophic hair follicles and hair. In most places the lining of the cyst had disappeared. In other areas there was a low, flattened squamous epithelium.

*Brain* The hemorrhage and the destruction of the adjacent tissues of the brain noticed grossly were accentuated microscopically. The blood had burrowed through the white matter but had not ruptured into the ventricle or surrounding perivascular spaces. In the region of the large hemorrhage there were rather numerous smaller, satellite hemorrhages and areas of fresh necrosis. The lateral portion of the internal capsule was necrotic. The putamen and globus pallidus were almost completely replaced by the clotted blood. The cerebral white matter in contact with the hemorrhage was necrotic and contained an infiltration of polymorphonuclear leukocytes, mononuclear cells and a small number of wandering phagocytic cells containing blood pigment. This picture was seen throughout the margin of the hemorrhage. In the anterior portion of the pons was another small area of fresh encephalomalacia, with a few polymorphonuclear leukocytes in it. The lateral ventricle, on the right side, contained a small number of leukocytes but no blood.

The small arteries showed all the degrees of sclerosis from slight thickening and fatty infiltration of the intima to complete calcification of the wall. Some of the vessels were nearly occluded by annular, sclerotic plaques. No thrombi were seen. The changes were more prominent in the vessels surrounding the hemorrhage. In the perivascular spaces also were small numbers of polymorphonuclear leukocytes. These too were more abundant in the region of the hemorrhage.

The meninges were only slightly thickened but contained diffusely scattered or occasionally clumped polymorphonuclear leukocytes. These were most numerous in the meninges over the right convexity, and the right side of the pons and cerebellum. They were seen to a lesser degree over the convexity of the unaffected left cerebral hemisphere. Fairly numerous large mononuclear cells also were present. There was no hemorrhage in the meninges. Bacterial stains did not reveal the presence of organisms. While the slight inflammatory changes in the substance of the brain about the hemorrhage were probably due to the destruction of the brain tissue, part or most of the meningeal infiltration cannot be interpreted as such, because of the injections of serum.

*Anatomic Diagnosis*—Arteriosclerosis was generalized but was especially marked in the small cerebral vessels. A massive cerebral hemorrhage occupied the right parietal and frontal lobes. There was evidence of aseptic meningitis, cerebral and spinal, which had followed intraspinal injection of serum. Slight lobular pneumonia, chronic cystitis and pyelitis, bilateral dermoid cysts of the ovaries and sickle cells were observed in the spleen.

*CASE 2*—A 61 year old Negress, complaining of headache of two weeks' duration, with a history of right hemiparesis and of hypertension, had a blood pressure of 228 systolic and 126 diastolic, residual right hemiparesis, a positive Wassermann reaction and polymorphonuclear leukocytosis in the spinal fluid,

with a count of 1,600 cells, of which 85 per cent were polymorphonuclear neutrophils and 15 per cent lymphocytes. While in the hospital she became delirious, and cervical rigidity developed. Her temperature rose to 104 F. She became stuporous and died on the tenth day in the hospital. Autopsy revealed multiple old and recent areas of encephalomalacia due to cerebral thrombosis.

CASE 3—A 64 year old white woman, with a history of hypertension, experienced tingling in the right arm and leg and subsequently lost consciousness. She presented elevation of temperature, a blood pressure of 260 systolic and 120 diastolic, moderate cervical rigidity, a turning of the head and eyes to the left, complete right hemiplegia and a cloudy spinal fluid containing 2,200 leukocytes, 86 per cent of which were polymorphonuclears. The fluid later became clear and showed only 8 lymphocytes. The patient regained consciousness on the fifth day in the hospital, but showed motor aphasia. She died of terminal bronchopneumonia. No autopsy was performed.

CASE 4—A 49 year old Negro, with a history of abdominal pain and delirium, presented an enlarged heart and auricular fibrillation, with normal reactions on neurologic examination. On the second day he became stuporous, and cervical rigidity developed. The spinal fluid was cloudy and contained 890 leukocytes, of which 95 per cent were polymorphonuclears. The cells disappeared in three days. Later left hemiplegia developed, and the patient died on the twelfth day in the hospital. Autopsy disclosed arteriosclerotic disease of the heart, mural thrombi, multiple visceral infarcts and embolism or thrombosis of the right middle cerebral artery with a large hemorrhagic infarct in the right temporal lobe.

CASE 5—A 64 year old white man with right hemiplegia and aphasia of four days' duration presented Cheyne-Stokes respirations, slight cervical rigidity, right hemiplegia, and a cloudy spinal fluid with moderate polymorphonuclear leukocytosis (472 leukocytes). The cells practically disappeared from the spinal fluid in five days. No clinical improvement was noted, and the patient died on the sixteenth day in the hospital. No autopsy was performed.

CASE 6—A 60 year old Negro with a history of headaches and dizzy spells became unconscious a few hours before admission. He was stuporous, with cervical rigidity, a positive Kernig sign, hypertension and arteriosclerosis, left hemiplegia and hemianesthesia involved mainly the face and arm. Serologic tests gave negative results. The spinal fluid was cloudy, with 1,000 polymorphonuclear leukocytes, these disappeared gradually, and a slight mononuclear response followed. Consciousness and motor function gradually returned.

#### REVIEW OF THE LITERATURE

Since 1891, when Quinke performed the first lumbar puncture and cleared the way for study of the cerebrospinal fluid, various observations have been made on the occasional occurrence of polymorphonuclear leukocytosis in cases of acute cerebral softening due to various causes mechanical in nature. The literature contains relatively little information on leukocytosis in association with cerebral hemorrhage and thrombosis.

The earliest observations are to be found in the French literature. In 1902 Widal and Lemaire<sup>1</sup> reported 2 cases of dementia paralytica with lymphocytic reaction in the spinal fluid in which the sudden development of hemiplegia was followed by marked polymorphonuclear responses. In 1 case the leukocytosis disappeared with recovery from the cerebral accident, while in the other autopsy revealed a massive intracerebral hemorrhage bordering on the lateral ventricle. In 1911 Claude and Verdun<sup>2</sup> reported the case of a 62 year old man with sudden onset of coma and a meningeal syndrome but no localizing signs. The spinal fluid was turbid and contained a predominance of polymorphonuclear cells. He was treated for meningitis but subsequently died, at which time autopsy revealed an old hemorrhage in the occipital lobe and a more recent hemorrhage in the parietotemporal region with no evidence of septic meningitis. Rendu and Flandin<sup>3</sup> in 1912 reported a case of cerebral hemorrhage in which two successive episodes were associated with meningeal phenomena, both clinical and cytologic. In the same year Babinski and Gendron<sup>3</sup> reported 3 cases of polymorphonuclear leukocytosis. Two of these were cases of cerebral embolism secondary to rheumatic heart disease. Eschbach,<sup>4</sup> Claude,<sup>1</sup> Oury<sup>1</sup> and Globus and Strauss<sup>4</sup> subsequently added other cases of thrombosis and hemorrhage in which the same characteristics were presented and several patients showed signs of meningeal irritation.

The first thorough review of the subject was made by Claude and Oury<sup>5</sup> in 1923. They classified the different types of meningeal reaction, discussing those particularly associated with focal lesions of the brain, and reviewed all the cases previously reported. They stated that in these aseptic meningeal reactions the cell counts may vary from 40 to 10,000 polymorphonuclear cells per cubic millimeter and that serial punctures show a decrease in the number of cells corresponding to the clinical improvement.

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1 Cited by Claude and Oury<sup>5</sup>

2 Claude, H., and Verdun, M. Syndrome meninge subaigu avec reaction leucocytaire aseptique du liquide cephalo-rachidien au cours des hemorrhagies cerebrales frustes sous-ependymo-corticales, *Bull et mem Soc med d hôp de Paris* **32** 68, 1911.

3 Babinski, J., and Gendron, A. Leucocytose du liquide cephalo-rachidien au cours du ramollissement de l'écorce cerebrale, *Bull et mem Soc med d hôp de Paris* **33** 370, 1912.

4 Globus, J. H., and Strauss, I. Vascular Lesions and Tumors of the Brain. Difficulties in Differential Diagnosis, *Arch Neurol & Psychiat* **15** 568 (May) 1926.

5 Claude, H., and Oury, P. Reactions meningees et epandements meninges puriformes aseptiques au cours des lesions en foyer de l'encephale, *Gaz d hôp* **96** 717, 1923.

In 1931 Cone and Baireira<sup>6</sup> reported the experimental production of cerebral infarcts in dogs by the injection of sterile emboli into the carotid arteries. Twenty dogs showed clinical signs of cerebral embolism, and in all these there was polymorphonuclear infiltration of the infarcts and surrounding areas, the earliest study being made eight and one-half hours after the insult. In 6 of the dogs neutrophils were seen in the spinal fluid at the time of death, the counts ranging from 371 at twenty-four hours to 1,135 at seventy-two hours after the occurrence of embolism. They concluded that polymorphonuclear cells pour into the infarcted area of the brain and overlying meninges within eight and a half hours after the occlusion of a vessel and reach their maximum at forty-eight hours. These cells reach the spinal fluid by way of the perivascular spaces, by direct invasion of the subarachnoid space or by extension into the ventricles.

Merritt and Fremont-Smith,<sup>7</sup> discussing alterations in the spinal fluid, stated that, in addition to inflammatory processes, various lesions associated with degeneration of the central nervous system, especially in proximity to the ventricular or subarachnoid surfaces, may be associated with slight or even moderate leukocytosis. High counts, however, are rare, but they cited 6 of 14 cases in which clear fluids showed white cell counts ranging from 50 to 1,900 polymorphonuclear cells.

#### COMMENT

When a stuporous or delirious patient with signs of meningeal irritation is found to have a great increase in cells in the spinal fluid, especially if the cells are predominantly polymorphonuclear, one naturally thinks first of some form of acute meningitis, and the tendency is to treat the condition as such, even when organisms cannot be demonstrated either by smear or by culture. It is not generally recognized, however, that acute cerebral softenings resulting from noninfectious causes sometimes give the same clinical picture. The present paper reports 6 cases of vascular lesions of the brain in which signs of meningeal irritation were present and the spinal fluid showed large numbers of polymorphonuclear cells but no red blood cells or only negligible numbers of the latter. In none of these cases was there definite clinical or postmortem evidence of an infectious process.

The first case is similar to that described by Claude and Veidun,<sup>2</sup> namely, there were a sudden onset of coma and a meningeal syndrome

6 Cone, W., and Barrera, S. E. The Brain and Cerebrospinal Fluid in Acute Aseptic Cerebral Embolism. Experimental and Pathologic Study, *Arch Neurol & Psychiat* 25 523 (March) 1931.

7 Merritt, H. H., and Fremont-Smith, F. The Cerebral Spinal Fluid, in Nelson Loose-Leaf Living Medicine, New York, Thomas Nelson & Sons, 1926, 1934, p. 555L.

but no localizing signs. The spinal fluid was turbid and contained a predominance of polymorphonuclear cells. The patient was treated for meningitis and died, and autopsy revealed a massive cerebral hemorrhage in the right parietal and frontal lobes (see figure, *A*).

The second case was one of infarction, multiple in nature, but localizing signs suggested a vascular accident. Later a meningeal syndrome developed, and meningitis was considered. On this occasion, however, our previous experience aided materially in making a correct diagnosis, which was borne out by postmortem examination.



Coronal sections of the brain (*A*, case 1, *B*, case 4), showing a large excavation in the right cerebral hemisphere filled with a blood clot. In case 1 there was no evidence of escape of blood into the ventricle. In case 4 the brain tore readily on its removal, as the cortex overlying the area of hemorrhage was thin. (The photographs were taken by permission of Mr. Milton Kough.)

The fourth case is somewhat similar to the first, except that signs of hemiplegia eventually developed and a diagnosis of vascular accident was made. Autopsy showed an infarct in the right temporal lobe due to thrombosis of the right middle cerebral artery. It is to be noted that the cells disappeared from the spinal fluid before death.

In cases 3, 5 and 6 localizing signs occurred, plus similar leukocytosis in the spinal fluid, and in view of our previous experience we feel justified in considering them similar to the 3 cases in which postmortem examinations were made.

Some idea of the frequency of this phenomenon may be deduced from the fact that during the period covered by our observations, approximately nine months, 43 patients were admitted to the Baltimore City Hospitals who had had cerebral accidents recently (i.e., not over a week before) and in whom signs of meningeal irritation or changes in the spinal fluid were lacking. Our 6 cases thus represent an incidence of approximately 12 per cent of the group in which the findings might be expected.

From these cases and similar ones described by others, it seems that in cases of vascular lesions of the brain, whether hemorrhage or thrombosis, the clinical manifestations may be variable, ranging from an acute meningeal syndrome to localizing signs and a history compatible with cerebral vascular accident, with leukocytosis revealed only by lumbar puncture. The spinal fluid in these cases may show an abundant cellular response with polymorphonuclear leukocytes, giving a cloudy fluid suggestive of meningitis, or only a microscopic reaction, with polymorphonuclears or a low mononuclear count. Serial punctures in the course of the illness will show a gradual decrease in the number of cells, and the spinal fluid may eventually become normal. In cases in which only mononuclear cells appear, the "purulent" stage has been missed, and the fluid is returning to normal, or the meningeal reaction has been slight from the beginning.

In view of the experimental work of Cone and Barrera,<sup>6</sup> it seems fair to explain these meningeal reactions on the basis of leukocytic response around the focus of softening or hemorrhage. These cells probably reach the perivascular spaces, the subarachnoid space or the ventricles, according to the location of the lesion. When the lesion is small and deeply situated the cells probably never get to the periphery, and consequently the spinal fluid remains clear.

In the cases in which postmortem examination was performed, the necrotic regions showed a varying degree of infiltration with polymorphonuclear leukocytes, mononuclear cells and a small number of wandering phagocytes containing blood pigment. Our first patient, who died early in the course of her illness, showed the greatest degree of infiltration with polymorphonuclear leukocytes. The meningeal reaction in her case was probably augmented by administration of anti-meningococcus serum.

It is to be expected that observations in these cases should fall in line with the experimental data already mentioned and that after the

vascular accident polymorphonuclear cells should pour into the affected area. Hence, postmortem examination during the early phase would show a predominantly polymorphonuclear infiltration, while during the later phases the infiltration would consist of mononuclear and phagocytic cells.

#### SUMMARY

Six cases of cerebral softening and cerebral hemorrhage in which a great excess of polymorphonuclear leukocytes was found in the spinal fluid are described.

We believe that this leukocytosis is due to an aseptic meningeal reaction to adjacent areas of necrosis within the brain.

It is only in cases in which the lesion is close to the surface of the cortex or approaches the wall of the ventricle that leukocytosis occurs, for deeply seated lesions cause no such reactions in the spinal fluid.

The leukocytosis usually begins within several hours after the infarction and gradually disappears within the next five to six days. The number of cells varies between 50 and 3,000 or more per cubic millimeter.

In cases in which the leukocytosis is great there may be stiffness of the neck and a positive Kernig sign, i. e., clinical evidence of meningeal irritation.

In cases in which the vascular lesion does not cause demonstrable focal signs leukocytosis of this type in the spinal fluid may result in an erroneous diagnosis of meningitis.

Other writers have made similar observations, and a brief discussion of the literature is appended.

The cases are published by permission of Dr. T. R. Boggs.

NOTE—Since completion of our study a case similar to those we have described was brought to our attention. By permission of Drs. W. T. Longcope and W. G. MacCallum, we give a brief summary of this case from the medical service of the Johns Hopkins Hospital.

H. R., a 35 year old woman, had a sudden onset of blindness, followed by gradually developing stupor. She showed signs of left hemiplegia. The spinal fluid on her admission was normal, but four days later cervical rigidity and a positive Kernig sign developed. The lumbar puncture was not repeated, but at autopsy a thick, purulent exudate in the meninges overlay the occipital lobes and the anterior surface of the cerebellum on both sides. Areas of encephalomalacia were noted beneath these exudates in the occipital lobes, in the cerebellum and also in the right internal capsule. There was extreme cerebral arteriosclerosis, but no large thrombosed vessel was observed to account for the infarcts. Microscopically the exudate, which consisted entirely of polymorphonuclear leukocytes, was seen to extend into numerous sulci and to involve the superficial portion of

the cortex and the perivascular spaces of the small vessels to the underlying parenchyma. Cultures of the blood and the cerebrospinal fluid, as well as bacterial stains of the exudate, failed to reveal any organisms.

We believe that this case falls into the group which we have discussed and that if a lumbar puncture had been done at the time when meningeal signs developed, it would have shown the presence of polymorphonuclears in the fluid. The case is of particular interest in that the course of the cells was traced directly from the softened areas of the brain, via the perivascular spaces and overlying cortex, to the subarachnoid space.



# STUDIES OF UROBILINOGEN

## I A SIMPLE AND RAPID METHOD FOR QUANTITATIVE DETERMINATION OF UROBILINOGEN IN STOOL AND IN URINE

ROBERT SPARKMAN, MD

CINCINNATI

Estimations of the urobilinogen content of stool and of urine afford information regarding the state of hepatic function, the patency of the extrahepatic biliary passages and the rate of destruction of red cells

The potential clinical value of estimations of urobilinogen has generally been inadequately realized. This has been due in large part to the lack of a method sufficiently simple and rapid to be within the scope of the average clinical laboratory and yet sufficiently accurate to afford dependable results

No attempt will be made to review the numerous procedures which have been devised for the quantitation of urobilinogen. This information may be obtained from the reviews and methods of Wilbur and Addis,<sup>1</sup> Terwen,<sup>2</sup> Wallace and Diamond,<sup>3</sup> Elman and McMaster,<sup>4</sup> Watson,<sup>5</sup> Scott,<sup>6</sup> Naumann<sup>7</sup> and Fairmer.<sup>8</sup>

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This work was aided by a grant from the Fraser Fund

From the Laboratories of Baylor University Hospital, Department of Pathology, Baylor University College of Medicine, Dallas, Texas

1 Wilbur, R. L., and Addis, T. Urobilin. Its Clinical Significance, *Arch Int Med* **13** 235 (Feb) 1914

2 Terwen, A. J. L. Ueber ein neue Verfahren zur quantitative Urobilin Bestimmung im Harn und Stuhl, *Deutsches Arch f Klin Med* **149** 72 (Nov) 1925

3 Wallace, G. B., and Diamond, J. S. The Significance of Urobilinogen in the Urine as a Test of Liver Function, *Arch Int Med* **35** 698 (June) 1925

4 Elman, R., and McMaster, P. D. The Quantitative Determination of Urobilin, *J Exper Med* **41** 503 (April) 1925

5 Watson, C. J. (a) The Average Daily Elimination of Urobilinogen in Health and Disease, with Special Reference to Pernicious Anemia, *Arch Int Med* **47** 698 (May) 1931, (b) Studies of Urobilinogen. I An Improved Method for the Quantitative Estimation of Urobilinogen in Urine and Feces, *Am J Clin Path* **6** 458 (Sept) 1936, (c) II Urobilinogen in the Urine and Feces of Subjects Without Evidence of Disease of the Liver or Biliary Tract, *Arch Int Med* **59** 196 (Feb) 1937, (d) III Per Diem Excretion of Urobilinogen in the Common Forms of Jaundice and Disease of the Liver, *ibid* **59** 206 (Feb) 1937

6 Scott, L. D. A Colorimetric Method for the Estimation of Urobilinogen in Urine and Feces, *J Lab & Clin Med* **18** 399 (Jan) 1933

*(Footnotes continued on next page)*

For accuracy of results, the method devised by Watson<sup>5b</sup> is unquestionably superior to any previously described. It has been modified by Naumann<sup>7b</sup>. Although much information regarding the physiologic and pathologic variations of urobilinogen of the stool and urine has been disclosed by the investigations of Watson,<sup>5</sup> the method employed is unsuited to general clinical use because of technical difficulty.

The method which has received the widest clinical acceptance is that of Wallace and Diamond.<sup>3</sup> This determination, however, is only roughly quantitative and is not well suited to estimation of urobilinogen in the stool.

A procedure is herewith presented for the quantitative determination of the urobilinogen of stool and urine. This method, because of its speed, simplicity and accuracy, is within the scope of any clinical laboratory and is therefore well adapted to clinical use.

#### METHOD

The method of estimating values of urobilinogen in stool and urine is dependent on the so-called aldehyde reaction, with the development of a red color on the addition of an acid solution of paradimethylaminobenzaldehyde (Ehrlich's aldehyde reagent) to solutions containing urobilinogen. This color is compared with an artificial standard prepared from gold chloride and sodium bromide.

The method of determining the urobilinogen of stool consists of aqueous emulsification of a weighed sample of stool, with reduction of urobilin to urobilinogen by ferrous sulfate and sodium hydroxide. The reduction is accelerated by incubation. This is followed by filtration, addition of Ehrlich's reagent and colorimetric comparison with the artificial standard after a suitable period has been allowed for the development of color.

Determination of the urobilinogen of urine is performed on fresh or suitably preserved specimens of urine, it consists of removal of bile pigment by addition of calcium chloride and filtration, with subsequent addition of Ehrlich's reagent to the filtrate. The residue on the filter is used in testing for bile pigment.

*Aldehyde Reagent*—The aldehyde reagent consists of a solution of paradimethylaminobenzaldehyde in hydrochloric acid. The dilution of reagent employed, described by Wilbur and Addis,<sup>1</sup> is prepared as follows. Seventy-five cubic centimeters of concentrated hydrochloric acid and 75 cc of distilled water are mixed and added to 10 Gm of paradimethylaminobenzaldehyde. A sample of reagent prepared in this manner has shown no deterioration after eight months.

*Artificial Standards*—An artificial standard is prepared by the addition of a solution of sodium bromide to a solution of gold chloride. Three strengths of this standard are employed. The three dilutions cover the range of most determinations of both fecal and urinary urobilinogen. The color is suitable for comparison with

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7 Naumann, H. N. (a) Studies on Bile Pigments. I. A Study of Ehrlich's Test for Urobilinogen and Schlesinger's Reaction for Urobilin, *Biochem J* **30** 347 (March) 1936, (b) III. The Quantitative Determination of Urobilin and Urobilinogen in Urine and Feces, *ibid* **30** 1021 (June) 1936.

8 Farmer, L. A Method for the Quantitative Determination of Urobilinogen in the Urine, *J. Lab. & Clin. Med.* **22** 1277 (Sept.) 1937.

aqueous and urinary solutions and with fecal extracts of urobilinogen. The following stock solutions are prepared: (1) a 4 per cent aqueous solution of gold chloride and (2) a 10 per cent aqueous solution of sodium bromide.

The three dilutions of standard are prepared from the stock solutions as follows:

1 **Strong Standard** One volume of sodium bromide is added to 1 volume of gold chloride, and the resultant solution is made up to 15 volumes with distilled water.

2 **Intermediate Standard** This standard is prepared by dilution of 1 volume of the strong standard with an equal volume of distilled water.

3 **Weak Standard** The weak standard is prepared by dilution of 1 volume of the intermediate standard with an equal volume of distilled water.

Samples of these standards have shown no deterioration after eight months.

*Evaluation of Standards in Terms of Crystalline Urobilinogen*—The values for the different strengths of standard in terms of milligrams of urobilinogen were determined by colorimetric comparison with known quantities of urobilinogen dissolved in weak solutions of sodium carbonate and treated with Ehrlich's reagent.

Crystalline urobilinogen was prepared from bilirubin (Eastman) according to the method of Fischer.<sup>9</sup> The product was identified by its physical and spectro-

TABLE 1.—*Evaluation of Standards in Terms of Crystalline Urobilinogen*

Standardization	Value of Standard, Mg per 100 Ce		
	Weak	Intermediate	Strong
First	0.966	2.730	8.950
Second	0.914	2.000	7.400
Average of first and second	0.935	2.365	8.175

scopic characteristics. The urobilinogen was weighed accurately and dissolved in a 0.5 per cent solution of sodium carbonate. Varying dilutions were prepared from the original solution of urobilinogen. To 10 cc of each dilution 1 cc of Ehrlich's reagent was added. Each of the three strengths of standard was compared in the colorimeter with the dilution of urobilinogen most closely resembling it in color, and the value of the standard in milligrams of urobilinogen per hundred cubic centimeters was computed therefrom. Crystalline urobilinogen was prepared a second time, and the standardization was repeated. The final values for the three standards were obtained by averaging the results determined on the two occasions. All procedures were carried out immediately after the preparation of crystalline urobilinogen and were performed in a subdued light. The results are recorded in table 1. Considering the instability of urobilinogen and the difficulty of its preparation, the figures for the two standardizations are in fairly close agreement.

As indicated by the figures in table 1, the values computed for the various standards are as follows: (a) strong standard, 8.175 mg of urobilinogen per hundred cubic centimeters, (b) intermediate standard, 2.365 mg, and (c) weak standard, 0.935 mg.

For ease of calculation these figures were simplified to the nearest first decimal. The final values for the standards are therefore as follows: (a) strong standard, 8.2 mg of urobilinogen per hundred cubic centimeters, (b) intermediate standard, 2.4 mg, and (c) weak standard, 0.9 mg.

<sup>9</sup> Fischer, H. Zur Kenntnis der Gallenfarbstoffe, *Ztschr f physiol Chem* 73: 204, 1911.

PROCEDURE FOR THE QUANTITATIVE DETERMINATION OF  
FECAL UROBILINOGEN

It is not essential that the determination be performed on fresh stool, since a stage is included whereby urobilin is reduced to urobilinogen. Stool should not be permitted, however, to undergo excessive desiccation. It is possible to perform determinations either on a single stool, expressing the result in terms of the concentration of urobilinogen in milligrams per hundred grams of stool, or on entire specimens collected over twenty-four or more hours, in which case the values for fecal urobilinogen may be expressed in terms of milligrams per twenty-four hour excretion. In this series of papers the former terminology is employed, for reasons which will be elaborated in the second article. The method for reduction of urobilin to urobilinogen is based on the procedure of Terwen<sup>2</sup> and its modifications by Watson<sup>5</sup> and Naumann<sup>7b</sup>. The detailed procedure for the quantitative determination of fecal urobilinogen follows.

Weigh 5 Gm of the mixed stool on a wooden tongue depressor and, with the aid of a small shiver of wood, transfer it to a mortar. Emulsify the stool in 100 cc of distilled water by gradual addition of the water and repeated transfer to a 250 cc Erlenmeyer flask. Dissolve 8 Gm of crystalline ferrous sulfate in 40 cc of water and transfer, with mixing, to the emulsion of stool (this reagent should be freshly prepared). Add slowly 40 cc of a 10 per cent solution of sodium hydroxide, rotating the flask during the addition. Stopper the flask and mix the contents by vigorous shaking. Place the flask and its contents in a water bath at a temperature of 50 C. Allow the flask to remain there fifteen minutes. Remove the mixture from the water bath and allow it to cool to room temperature, then filter (Whitman no 2 filter paper is satisfactory). Pipet 5 cc of the filtrate into a test tube. Add 5 cc of distilled water, 0.3 cc of five times normal hydrochloric acid and 1 cc of Ehrlich's reagent. Allow five minutes for full development of the color. Compare the solution in a colorimeter with the standard of the nearest depth of color. The unknown solution should be read promptly after being placed in the colorimeter cup. Calculations are made as follows<sup>10</sup>: (a) If the strong standard is used,  $R_s/R_u \times 630$  represents the number of milligrams of urobilinogen per hundred grams of stool, (b) if the intermediate standard is used, the formula is  $R_s/R_u \times 185$ , and (c) if the weak standard is used, the formula is  $R_s/R_u \times 70$ . The three standards cover all ranges of values for urobilinogen with the exception of extremely high ones. In the event that such concentrations are encountered, the procedure is repeated after suitable dilution of the filtrate.

*Comment*—With the method proposed by Watson<sup>5b</sup> one hour is allowed for the reduction of urobilin to urobilinogen. This reduction

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<sup>10</sup> The numerical factors for the calculations listed are obtained in the following manner. The mixture of stool, water, ferrous sulfate and sodium hydroxide has an approximate volume of 187 cc. When the final addition of 5 cc of water and 0.3 cc of hydrochloric acid to 5 cc of fecal filtrate is taken into account, the ultimate solution prior to the addition of Ehrlich's reagent represents 5 Gm of stool in approximately 385 cc of solution. The concentration of urobilinogen in milligrams per hundred grams of stool is therefore calculated by the formula,  $\text{urobilinogen} = R_s/R_u \times F \times 3.85 \times 20$ , in which  $F$  represents the urobilinogen equivalent of the particular strength of standard which is employed. The value for  $F$  is 82, 24 and 0.9 for the strong, the intermediate and the weak standard, respectively.

is allowed to proceed at room temperature Naumann<sup>7b</sup> presented evidence to indicate that the reduction is dependent on the time factor, the reducing action reaching a peak in three hours at 20 C or in five minutes at 35 C In order to verify the acceleration of reduction at increased temperatures, 10 samples of stool were analyzed after they had been in the water bath for fifteen minutes at 50 C and after they had stood for three hours at room temperature The results of this study, which are presented in table 2, indicate that full reduction is obtained in the allotted period of incubation, supporting the statements made by Naumann

The characteristic color reaction occurring on addition of Ehrlich's reagent to urobilinogen is due to the pyrrole group The same color may be obtained by addition of Ehrlich's reagent to indole, which also

TABLE 2—*Effect of Incubation on Reduction Time of Urobilinogen*

No of Specimen of Stool	Concentration of Urobilinogen After 15 Minutes in Water Bath at 50 C, Mg per 100 Gm	Concentration of Urobilinogen After 3 Hours at Room Temperature, Mg per 100 Gm
1	215.6	212.4
2	212.4	206.5
3	222.6	222.6
4	81.0	81.4
5	254.5	276.0
6	206.5	224.2
7	228.4	238.6
8	162.3	166.7
9	187.0	184.0
10	96.0	91.0

possesses a pyrrole group Indole is produced in the intestine by the action of putrefactive bacteria on protein, it is generally regarded as the fecal constituent most likely to induce error in determinations of fecal urobilinogen Indole is very slightly soluble in water at room temperature, moderately soluble in hot water and readily soluble in ether or alcohol In methods involving extraction of urobilinogen with ether or purified petroleum benzine it is necessary to include some process for avoiding the effect of indole This is ordinarily accomplished by bringing about the aldehyde reaction in a medium of acetic acid rather than hydrochloric acid Naumann,<sup>7b</sup> however, stated the belief that this expedient prevents only a part of the color produced by indole With my method, owing to the relative insolubility of indole in aqueous solutions at room temperature, the degree of interference is slight and of little clinical significance Convincing evidence of this fact has been obtained by analysis of 30 specimens of stool from 5 patients who were subsequently proved to have complete obstruction

of the common duct, which prevented any bile from reaching the intestine. In every instance color was absent after the addition of Ehrlich's reagent, a fact which effectively established the absence of both indole and urobilinogen. The small amount of bile which reaches the gastrointestinal tract from its bile-stained mucosa is insufficient to give a positive reaction in the test for urobilinogen with the method described.

In addition to the clinical evidence just cited, which indicated the negligible effect of indole, experimental evidence which led to the same conclusion was established. With the use of alcoholic solutions of indole it was found that on addition of Ehrlich's reagent the intensity of color produced per milligram of indole approximates that produced by an equal weight of urobilinogen. A saturated aqueous solution of indole, however, when treated with Ehrlich's reagent produces a color equivalent to that caused by only 0.9 mg of urobilinogen per hundred cubic centimeters. Indole was added to four portions of a sample of acholic stool in such quantities as to produce a concentration of 100, 200, 300 and 400 mg of indole per hundred grams of stool, respectively. On subsequent analysis of these specimens of stool, the degree of color produced was equivalent to that caused by only 53.4, 56, 60.6 and 61.3 mg of urobilinogen per hundred grams of stool, respectively.

It is thereby demonstrated that with my method indole is capable of producing some interfering effect but that the degree of interference is extremely slight and is apparently limited by the extent of the aqueous solubility of indole. Moreover, the results obtained from analysis of 30 samples of stool from 5 patients who had complete obstruction of the common bile duct indicate that the percentage of error induced by indole in clinical analysis is even considerably less than the small amount which can be produced experimentally.

#### PROCEDURE FOR QUANTITATIVE DETERMINATION OF URINARY UROBILINOGEN AND DETECTION OF BILE PIGMENT IN URINE

The method is applicable either to single specimens of urine or to specimens excreted during twenty-four hours or more. Single samples should be freshly voided. Twenty-four hour specimens are collected according to the method advocated by Watson,<sup>5b</sup> which consists of the employment of a brown glass bottle to which has been added about 100 cc of purified petroleum benzine and 5 Gm of anhydrous sodium carbonate. The details of the procedure follow.

To a small amount of urine in a flask add anhydrous calcium chloride in the proportion of 50 cc of urine to 2 Gm of the salt. Mix the combination well and filter. The residue on the filter is used in the detection of bile pigment, while the filtrate is used for the quantitative determination of urobilinogen.

*Test for Bile Pigment*—Pour a few drops of concentrated nitric acid down the side of the filter. In the presence of bilirubin a colored zone is produced which consists of a central area of pink (choletelin) and a periphery of green (biliverdin). As much as five minutes may be necessary for full development of the color.

*Determination of Urobilinogen*—Add 1 cc of Ehrlich's reagent to 10 cc of the filtrate and mix by several inversions. Allow five minutes for full development of the color. Match the sample promptly in a colorimeter with the standard which has the intensity of color nearest that of the unknown solution. With specimens containing unusually high concentrations of urobilinogen the procedure is repeated after suitable dilution of the filtrate. Calculations are made as follows: (a) When the strong standard is employed,  $R_s/R_u \times 82$  represents the number of milligrams of urobilinogen per hundred cubic centimeters of urine, (b) when the intermediate standard is employed, the formula is  $R_s/R_u \times 24$ , and (c) when the weak standard is employed, the formula is  $R_s/R_u \times 0.9$ .

*Comment*—The test for bile pigment is a modification of the Gmelin test. Concentration of bile pigment occurs through adsorption

TABLE 3—*Relative Sensitivity of Standard Tests for Bile Pigment in Urine\**

Dilution of Urine	Results of Tests					Adsorption with Calcium Chloride
	Foam	Gmelin	Rosenbach	Huppert	Huppert Cole	
None	Strongly positive	Strongly positive	Strongly positive	Strongly positive	Strongly positive	Strongly positive
1 10	Weakly positive	Weakly positive	Weakly positive	Positive	Weakly positive	Positive
1 20	Negative	Negative	Trace	Positive	Trace	Positive
1 40			Negative	Positive	Negative	Positive
1 80				Weakly positive		Weakly positive
1 160				Trace		Trace
1 320				Negative		Negative

\* Hawk, P. B., and Bergelm, O., and others. *Practical Physiological Chemistry*, ed 11, Philadelphia, P. Blakiston's Son & Co., 1937, p. 342.

to calcium chloride, which results in greatly increased sensitivity of the test. The sensitivity of this method was compared with that of standard methods by obtaining a specimen of urine which contained large amounts of bile and performing the various tests for bile pigments on progressively diluted portions of the original specimen. The results are recorded in table 3.

A simple and extremely sensitive test for bile pigment in the urine has been described by Naumann.<sup>11</sup> This is somewhat too sensitive for clinical purposes, however, since it demonstrates traces of bile even in normal urine. The sensitivity of the test just described seems well suited to clinical use. Significant quantities of bile can always be

11 Naumann, H. N. *Studies on Bile Pigments. II. A New Test for Bilirubin in the Urine and Its Use for Detection of Bilirubin in Normal Urine*, *Biochem J* 30:762 (May) 1936.

detected by this method, whereas other methods frequently fail to demonstrate the presence of bile

It is generally agreed that in freshly voided urine it is unnecessary to employ a reducing agent, since inconsequential amounts of urobilin are present, practically all the chromogen having the form of urobilinogen. Moreover, I have obtained evidence which indicates that in urine preserved according to the method of Watson previously described oxidation of urobilinogen to urobilin over twenty-four hours is so slight as to be of no clinical significance. To establish this fact, 5 samples of urine were preserved under the conditions previously enumerated, and after twenty-four hours the urobilinogen content of each was determined with and without reduction by ferrous sulfate and sodium hydroxide. Only specimens having an abnormally high content of urobilinogen were employed. In no instance was there a significant loss

TABLE 4—*Deterioration of Urobilinogen in Preserved Twenty-Four Hour Specimens of Urine*

No. of Specimen	Urobilinogen Content, Mg. per 100 Cc.	
	Without Reduction	After Reduction
1	11.71	11.78
2	7.13	7.25
3	10.45	8.82
4	20.50	19.22
5	9.11	10.21

of urobilinogen, as shown in table 4. For this reason no procedure is included for reduction of urobilin to urobilinogen in freshly voided or properly preserved urine.

Rarely, large quantities of protein in urine cause turbidity after the addition of Ehrlich's reagent. In such an instance the protein can be removed by mixing equal quantities of urine and a 3 per cent solution of sulfosalicylic acid and filtering.

#### GENERAL COMMENT

Filtrates obtained with the extraction of urobilinogen from feces are practically devoid of any pigment other than that due to urobilinogen, in consequence of which the method described is equally accurate for high or low concentrations of urobilinogen.

In performing estimations of urinary urobilinogen as a source of information of clinical value, one is primarily concerned only with increases in concentration. With the exception of the removal of bile pigment to avoid turbidity, no attempt is made to free the urine of its coloring matter. Thus the values for urinary urobilinogen in the normal



range will be higher than those obtained by other methods. As the concentration of urinary urobilinogen increases, diminution of the error induced by other urinary pigments occurs, the error being inconsequential when the pathologic range of urobilinogenuria is reached.

Methods employing extraction of urobilinogen by purified petroleum benzine or ether involve some loss of urobilinogen by incomplete extraction and by oxidation of the unstable chromogen on exposure to light. These sources of error are largely avoided with my method. Watson<sup>1b</sup> stated that in consequence of the instability of urobilinogen it is certain that no quantitative method can aspire to more than approximate values. This being true, any sources of error in the method described are more than offset by its speed and simplicity.

#### SUMMARY

A procedure is described for the quantitative determination of urobilinogen in stool and urine. The principal advantages of the method are simplicity, rapidity and clinical adaptability.

A sensitive test for bile pigment in the urine, consisting of a modification of the Gmelin test, is also described.

Dr Benjamin Wells, of the department of physiologic chemistry, prepared crystalline urobilinogen on two occasions, and Dr E. R. Hayes gave suggestions regarding the preparation of the artificial standards.

## STUDIES OF UROBILINOGEN

### II NORMAL VALUES FOR EXCRETION OF UROBILINOGEN IN SINGLE SPECIMENS OF URINE AND STOOL

ROBERT SPARKMAN, M D

CINCINNATI

In the first article of this series a simple method was described for the quantitative determination of urobilinogen in stool and urine. This method is applicable to the analysis either of single specimens of urine and stool or of specimens collected over twenty-four or more hours.

The remarkable investigations of Watson<sup>1</sup> constitute the most outstanding contribution to the knowledge of the daily excretion of urobilinogen in health and disease. It is his belief that examination of single specimens of urine and stool is of little aid in diagnosis and that the potential clinical value of studies on urobilinogen can be realized only by determination of the total daily excretion of urobilinogen in stool and urine. The procedure which he employs involves the collection of one or more twenty-four hour specimens of urine and of entire specimens of stool for at least four days.

The clinical value of any type of procedure which requires the prolonged collection of entire specimens of stool is subject to obvious limitations. The same is true in a limited sense of the repeated collection of twenty-four hour specimens of urine. The diagnostic value of estimations of urobilinogen on single specimens of urine, particularly in the detection of impaired hepatic function and in the differential diagnosis of jaundice, has been established by the investigations of Wallace and Diamond,<sup>2</sup> Piersol and Rothman,<sup>3</sup>

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This work was aided by a grant from the Fraser Fund.

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1 Watson, C. J. (a) The Average Daily Elimination of Urobilinogen in Health and Disease, with Special Reference to Pernicious Anemia, *Arch Int Med* **47** 698 (May) 1931, (b) Studies of Urobilinogen. I. An Improved Method for the Quantitative Estimation of Urobilinogen in Urine and Feces, *Am J Clin Path* **6** 458 (Sept) 1936, (c) II Urobilinogen in the Urine and Feces of Subjects Without Evidence of Disease of the Liver or Biliary Tract, *Arch Int Med* **59** 196 (Feb) 1937, (d) III Per Diem Excretion of Urobilinogen in the Common Forms of Jaundice and Disease of the Liver, *ibid* **59** 206 (Feb) 1937.

2 Wallace, G. B., and Diamond, J. S. The Significance of Urobilinogen in the Urine as a Test of Liver Function, *Arch Int Med* **35** 698 (June) 1925.

3 Piersol, G. M., and Rothman, M. M. Practical Value of Liver Function Tests, *J A M A* **91** 1768 (Dec 8) 1928.

Rosenberg<sup>4</sup> and White<sup>5</sup> Further evidence that significant clinical observations can be based on a knowledge of the concentration of urobilinogen in successive single specimens, particularly of stool, will do much toward placing this type of determination on a practical clinical basis

The present article describes a series of quantitative determinations of the urobilinogen content of single specimens of urine and feces The results of urinalysis are expressed in terms of the concentration of urobilinogen in milligrams per hundred cubic centimeters of urine The concentration of fecal urobilinogen is expressed in terms of milligrams of urobilinogen per hundred grams of stool

This study serves as a control for the method previously described and for the application of this method to clinical study, which will be dealt with in a subsequent article

#### MATERIAL AND METHODS

The method employed for the determination of fecal and urinary urobilinogen is that described in the first article of this series Color developed in fecal extract or in urine by the addition of Ehrlich's reagent is matched against an artificial standard prepared from gold chloride and sodium bromide Three dilutions of the standard, designated as the strong, the intermediate and the weak, are available The unknown solution is matched against the standard which it approximates most closely in intensity of color

The control series of tests included 100 determinations of fecal urobilinogen and 200 determinations of urinary urobilinogen Of the 100 samples of stool, 50 were obtained from ambulatory persons, apparently in good health, who represented all ages and both sexes The remaining 50 were obtained from hospital patients who presented no evidence of hepatic disease, jaundice or significant alteration in the state of balance between production and destruction of red cells The 200 specimens of urine consisted of two groups of 100 each, subdivided according to the same criteria

#### RESULTS

In the first group of 50 samples of stool, obtained from ambulatory subjects, the average excretion of urobilinogen was 259.1 mg per hundred grams of stool Seventy-two per cent of the values for this series were between 150 and 300 mg The highest and the lowest value encountered were 520 and 76.4 mg per hundred grams, respectively

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4 Rosenberg, D. H. Galactose and Urobilinogen Tests in Differential Diagnosis of Obstructive and Intrahepatic Jaundice, *Ann Int Med* 8:60 (July) 1934

5 White, F. W. Galactose and Urobilinogen Tests in the Differential Diagnosis of Painless Jaundice, *Am J Digest Dis & Nutrition* 4:315 (July) 1937

In the second group of specimens of stool, obtained from hospital patients, an average urobilinogen excretion of 201.9 mg per hundred grams was observed. Sixty-six per cent of the values for this series were between 150 and 300 mg. The highest and the lowest value encountered were 600 and 72.6 mg per hundred grams, respectively.

The composite of the two groups, representing 100 determinations, yielded a general average of 230.5 mg of urobilinogen per hundred grams of stool, with values lying between 150 and 300 mg in 69 per cent of the instances. Fifteen per cent of the results were below this range, while 16 per cent exceeded it.

The results are presented in table 1.

TABLE 1—*Quantitative Determinations of Urobilinogen in 100 Specimens of Stool*

Urobilinogen, Mg per 100 Gm of Stool	Number of Subjects	
	Ambulatory	In Hospital
Below 100	2	5
100-150	2	6
150-200	11	20
200-250	16	11
250-300	9	2
300-350	1	2
350-400	3	0
400-450	0	2
450-500	2	1
500-550	3	1
550-600	1	1
Representative Values, Mg per 100 Gm of Stool		
	Ambulatory	In Hospital
Average*	239.1	201.9
Highest	520.0	600.0
Lowest	76.4	72.6

\* General average for both groups, 230.5 mg per hundred grams of stool.

Values obtained for urobilinogen in normal urine with the method employed are higher than with other methods, since no attempt is made to remove the pigments of the urine. The interfering effect of such pigments becomes inconsequential when the pathologic range of urobilinogenuria is reached.

For the first series of 100 samples of urine, obtained from ambulatory subjects apparently in good health, the average value was 222 mg of urobilinogen per hundred cubic centimeters of urine. Ninety-six per cent of the specimens were in the color range of the weak or of the intermediate standard. For the remaining 4 per cent, which were in the color range of the strong standard, the highest value observed was 8 mg. Most of the specimens were voided in the afternoon.

The average for the second series of samples of urine, obtained from hospital patients, was 124 mg of urobilinogen per hundred cubic

centimeters of urine. The lower average is accounted for by the fact that most of the specimens in this group were voided in the morning, at which time the excretion of urobilinogen is at its lowest point. Ninety-eight per cent of the samples were in the color range of the weak or of the intermediate standard. For the remaining 2 per cent, which were in the color range of the strong standard, the highest value observed was 7.36 mg.

Of the composite group of 200 specimens of urine, only 6, or 3 per cent, were in the color range of the strong standard. No bile pigment was detected in any specimen.

Detailed results for the series are presented in table 2.

TABLE 2—*Quantitative Determinations of Urobilinogen in 200 Specimens of Urine\**

Urobilinogen, Mg. per 100 Cc.	Number of Subjects	
	Ambulatory	In Hospital
Below 1	22	54
1-2	17	33
2-3	47	10
3-4	10	1
4-5	0	0
5-6	0	0
6-7	1	1
7-8	3	1
Representative Values, Mg. per 100 Cc.		
	Value	
Average†	2.22	1.24
Highest	8.00	7.36

\* The urine of 4 ambulatory subjects and 2 patients yielded a color which matched that of the strong standard.

† General average for both groups, 1.73 mg. per hundred cubic centimeters.

#### COMMENT

Normal values for fecal urobilinogen obtained by my method usually lie between 150 and 300 mg. of urobilinogen per hundred grams of stool. The extreme limits of normal values are 70 to 600 mg. With this method, results for single specimens of stool are usually approximately twice those obtained with Watson's method<sup>1c</sup>. The lower values obtained by Watson's method are unquestionably due in part to loss of some urobilinogen, either by incomplete extraction or by exposure to light. Watson concluded that the normal range for feces is between 40 and 280 mg. per day, usually being from 100 to 250 mg. The normal variation of the urobilinogen concentration of single specimens of stool as ascertained by my method is little wider than the variation in daily excretion of fecal urobilinogen.

Any specimen of urine yielding a color in the range of the weak or of the intermediate standard may be regarded as containing no increase of urobilinogen. In such a case it is recommended that the value be reported as "not increased" rather than numerically, since other urinary pigments induce some error for urobilinogen values in the normal range. Colors in the range of the strong standard should be regarded with suspicion, particularly if associated with a positive reaction to the test for bile pigment. Values exceeding 8 mg per hundred cubic centimeters almost certainly represent pathologic urobilinogenuria.

#### SUMMARY

On the basis of results obtained by the examination of 100 specimens of stool and 200 specimens of urine, normal values have been established for the concentration of urobilinogen in urine and in stool according to the method described in the first article of this series.

# STUDIES OF UROBILINOGEN

## III CLINICAL VALUE OF DETERMINATIONS OF UROBILINOGEN CONTENT OF SINGLE SPECIMENS OF URINE AND STOOL

ROBERT SPARKMAN, M D

CINCINNATI

Three distinct types of clinical information can be derived from studies of fecal and urinary urobilinogen

Estimations of the urobilinogen of the stool constitute the best single measure of the rate of destruction of red cells. Increase of urobilinogen in the urine is one of the first manifestations of hepatic disease. Combined estimations of the urobilinogen of the stool and of the urine furnish one of the few dependable means of distinguishing between jaundice of intrahepatic origin and jaundice arising from obstruction of the extrahepatic biliary passages.

In spite of their potential value, studies of fecal and urinary urobilinogen have not come into general clinical use. This is readily understood when one realizes that most methods for the determination of urobilinogen require several days for the collection of specimens and several hours for the analytic procedures themselves.

In the first article of this series there was described a simple and rapid method for the quantitative determination of the urobilinogen of stool and urine. In the second article it was shown how this method was employed to establish normal values for the urobilinogen concentration of single specimens of urine and stool.

In the investigation reported here an attempt was made to apply the procedure previously described to the study of the three types of condition just mentioned and to demonstrate that with each type significant information can be obtained from analysis of single specimens of urine and stool rather than of specimens saved for several days.

The importance of urobilinogen in supplying evidence of disturbed hepatic function was first established by von Muller<sup>1</sup>. The investi-

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<sup>1</sup> von Muller, F. Ueber Ikterus, Jahresb d schles Gesellsch f vaterl Kult (Med Sekt) 70 1, 1893.

gations of Elman and McMaster<sup>2</sup> furnished much of the physiologic and pathologic basis on which has been developed the clinical application of studies on urobilinogen

Bilirubin is generally agreed to be derived from the hemoglobin of destroyed erythrocytes. This synthesis probably occurs in the reticulo-endothelial system. On reaching the intestinal tract, bilirubin is converted to urobilinogen by the action of intestinal bacteria. The greater part of the pigment is excreted in the stool, either as urobilinogen or as its oxidation product urobilin. That portion of the urobilinogen not excreted in the stool is absorbed and is carried to the liver by the portal circulation. Most of the urobilinogen which reaches the liver is reexcreted or utilized, the remaining small amounts entering the systemic circulation and being excreted as urobilinogen in the urine.

In the absence of impediment to the passage of bile from the liver to the intestine, the quantity of fecal urobilinogen parallels the rate of erythrocytic destruction. Estimations of fecal urobilinogen are therefore of value in the study of the anemias, especially in distinguishing anemias of increased destruction from those of decreased production.

The ability to reexcrete or to utilize the urobilinogen absorbed from the bowel is impaired relatively early in the course of disease of the liver, so that hepatic damage is associated with increased excretion of urobilinogen in the urine. Thus estimations of urinary urobilinogen afford a sensitive test for the presence of damage to the liver.

Total obstruction of the extrahepatic biliary passages, with complete failure of bile to reach the intestine, is associated with absence of urobilinogen from feces and urine. Partial obstruction is usually accompanied by diminution in fecal and urinary urobilinogen. Determinations of urinary and fecal urobilinogen thereby provide a means of differentiation between jaundice of intrahepatic origin and jaundice arising from complete or partial occlusion of the extrahepatic biliary passages.

Many investigators have contributed to knowledge of the clinical significance of determinations of urobilinogen. Relatively few of these studies, however, have been based on the examination of single specimens. Such work has been confined almost exclusively to the examination of urine alone.

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<sup>2</sup> Elman, R., and McMaster, P. D. Studies on Urobilin Physiology and Pathology. I. Quantitative Determination of Urobilin, *J. Exper. Med.* **41** 503 (April) 1925, II. Derivation of Urobilin, *ibid.* **41** 513 (April) 1925, III. Absorption of Pigments of Biliary Derivation from the Intestine, *ibid.* **41** 719 (June) 1925; IV. Urobilin and the Damaged Liver, *ibid.* **42** 99 (July) 1925, V. Relation Between Urobilin and Conditions Involving Increased Red Cell Destruction, *ibid.* **42** 619 (Nov.) 1925, VI. Relation of Biliary Infections to the Genesis and Excretion of Urobilin, *ibid.* **43** 753 (June) 1926.



The most comprehensive study of this type was that of Wallace and Diamond,<sup>3</sup> in which the examination of single specimens of urine was performed in 1,220 cases. Conditions associated with pathologic urobilinogenuria were subdivided into two groups. In the first group, consisting of diseases involving the liver and the biliary tract, increases of urinary urobilinogen were observed in cases of catarrhal jaundice, cholangitis, acute yellow atrophy, hepatic cirrhosis, chronic passive congestion of the liver associated with chronic endocarditis, abscess of the liver when the suppurative process was generalized rather than confined to a solitary lesion, miliary tuberculosis involving the liver, metastases producing generalized carcinomatosis of the liver rather than localized nodular areas, and toxic states, such as eclampsia. Absence of urobilinogen from the urine was noted in cases of complete obstruction of the bile passages due to neoplasm, and the value of determinations of urobilinogen in differentiating between jaundice arising from this cause and jaundice arising from hepatic disease was noted. In the second group, consisting of hemolytic diseases, pathologic urobilinogenuria was observed in cases of hemolytic icterus, pernicious anemia, septic states, malaria, lead poisoning and other types of hemolysis produced by poisons.

Piersol and Rothman<sup>4</sup> used single estimations of urinary urobilinogen in the detection of hepatic damage and in the differential diagnosis of jaundice; they concluded that estimation of the urobilinogen of the urine is probably the most delicate single test for dysfunction of the liver. Rosenberg<sup>5</sup> employed single specimens of urine and concluded that the determination of the urobilinogen of the urine provides the most reliable means of differentiating between hepatic and extra-hepatic types of jaundice. White<sup>6</sup> utilized estimations of the urobilinogen of single specimens of urine in the differential diagnosis of jaundice.

The studies of Elman and McMaster<sup>2</sup> were based on examination of twenty-four hour specimens of urine and stool. The same is true of the investigations of Wilbur and Addis.<sup>7</sup> These authors stressed the

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3 Wallace, G. B., and Diamond, J. S. The Significance of Urobilinogen in the Urine as a Test of Liver Function, *Arch Int Med* **35** 698 (June) 1925.

4 Piersol, G. M., and Rothman, M. M. Practical Value of Liver Function Tests, *J. A. M. A.* **91** 1768 (Dec 8) 1928.

5 Rosenberg, D. H. Galactose and Urobilinogen Tests in Differential Diagnosis of Obstructive and Intrahepatic Jaundice, *Ann Int Med* **8** 60 (July) 1934.

6 White, F. W. Galactose and Urobilinogen Tests in the Differential Diagnosis of Painless Jaundice, *Am J Digest Dis & Nutrition* **4** 315 (July) 1937.

7 Wilbur, R. L., and Addis, T. Urobilin. Its Clinical Significance, *Arch Int Med* **13** 235 (Feb.) 1914.

importance of fecal urobilinogen values as a guide to the amount of destruction of blood in the body. Increased excretion of urinary urobilinogen was noted in various types of damage to the liver, including hepatic cirrhosis, hepatic stasis, poisonings, acute yellow atrophy, pneumonia and infections. In cases of obstructive jaundice urinary urobilinogen was observed to be absent or insignificant. Its intermittent presence was interpreted as indicative of incomplete obstruction with concomitant damage to the liver. Increases of urobilinogen in urine and stool were noted in various hemolytic diseases.

The extensive investigations of Watson<sup>8</sup> furnished the most complete and exact information available regarding the excretion of fecal and urinary urobilinogen in health and disease. These studies were based on examination of ninety-six hour specimens of stool and repeated twenty-four hour specimens of urine. This author emphatically expressed his belief that estimations of urobilinogen are of little clinical value unless they express results in terms of twenty-four hour excretion. The studies of Watson confirmed and amplified previously known facts regarding the clinical significance of estimations of urobilinogen and disclosed in addition much new information of great value. Increases in fecal urobilinogen were noted in hemolytic diseases. In pernicious anemia a decrease of urobilinogen in stool and urine was observed to be coincident with reticulocytic response to liver therapy. Increased urobilinogen in the stool was observed in some instances of Hodgkin's disease and leukemia. Low values were encountered in cases of secondary hyperchromic anemia and in all the cases of hypochromic anemia investigated. The idea was expressed that increases of urinary urobilinogen associated with hemolytic jaundice were probably secondary to complicating hepatic damage. Jaundice due to stone was not accompanied by considerable increase in urinary urobilinogen unless complications were present, such as acute cholecystitis or cholangitis, biliary cirrhosis or severe anemia. With such a complication the actual amount of urobilinogen appearing in the urine was dependent to some extent on the degree of biliary obstruction and the consequent amount of urobilinogen formed in the bowel and released from it. Thus if obstruction was predominant urinary urobilinogen was diminished, whereas if the obstruction was slight and the hepatic damage

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8 Watson, C. J. (a) The Average Daily Elimination of Urobilinogen in Health and Disease, with Special Reference to Pernicious Anemia, *Arch Int Med* 47:698 (May) 1931, (b) Studies of Urobilinogen. I. An Improved Method for the Quantitative Estimation of Urobilinogen in Urine and Feces, *Am J Clin Path* 6:458 (Sept.) 1936; (c) II Urobilinogen in the Urine and Feces of Subjects Without Evidence of Disease of the Liver or Biliary Tract, *Arch Int Med* 59:196 (Feb.) 1937, (d) III Per Diem Excretion of Urobilinogen in the Common Forms of Jaundice and Disease of the Liver, *ibid* 59:206 (Feb.) 1937.

considerable urinary urobilinogen was increased. Jaundice due to neoplastic obstruction of the extrahepatic biliary passages was characterized by complete obstruction, as evidenced by persistent absence of urobilinogen from stool and urine. This was in contradistinction to jaundice due to stone or diffuse hepatic disease. The latter was usually characterized by marked increase of urobilinogen in the urine. In some cases cirrhosis was accompanied by signs of increased destruction of blood, such as increase in fecal urobilinogen and regenerative anemia, often macrocytic.

Josephs<sup>9</sup> made extensive use of estimations of the urobilinogen of the stool as a measure of erythrocytic destruction. In his studies of the anemias the amount of urobilinogen in the urine was disregarded, since he considered it to be negligible. The author employed two day specimens of stool. He stated the belief that a proper interpretation of values for fecal urobilinogen presupposes a knowledge of the amount of hemoglobin in the body.

The 40 cases in my series were divided in three groups. The first consists of cases in which the estimations of urobilinogen were employed for the detection of hepatic dysfunction. In none of these cases was there more than slight jaundice. The second group consists of cases of severe jaundice in which estimations of urobilinogen were used as a means of differential diagnosis of jaundice. The third group consists of cases in which there was some abnormality in either production or destruction of erythrocytes, in this group estimations of urobilinogen were employed primarily as a measure of destruction of red cells.

With my method, preparations of stool or urine are matched colorimetrically against one of three strengths of an artificial standard, which collectively cover the color range of most specimens. These are designated as the strong, the intermediate and the weak standard.

According to this method, normal values for stool are usually between 150 and 300 mg of urobilinogen per hundred grams of stool. The extreme limits of normal are 70 to 600 mg of urobilinogen per hundred grams of stool. Urine in the color range of the weak or the intermediate standard is regarded as containing no increase of urobilinogen. Urine requiring comparison with the strong standard should be regarded with suspicion. The extreme upper limit of values for normal urine is 8 mg of urobilinogen per hundred cubic centimeters.

#### A DETERMINATIONS OF UROBILINOGEN IN THE DETECTION OF HEPATIC DYSFUNCTION

This group consists of 19 cases in which clinical jaundice was slight or not demonstrable.

The employment of determinations of urobilinogen in the detection of hepatic dysfunction is dependent on the diminished ability of the damaged liver to utilize or reexcrete the urobilinogen which is absorbed

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<sup>9</sup> Josephs, H. W. Mechanism of Anemia in Infancy, *Bull. Johns Hopkins Hosp.* **51** 185 (Oct.) 1932, Urobilin Excretion of Infancy and Childhood. Relation to Blood Destruction and Formation, *ibid.* **55** 154 (Aug.) 1934.

from the bowel, as a result of which increased amounts of urobilinogen are excreted in the urine. Therefore estimations of urobilinogen for demonstration of impaired hepatic function are largely confined to examination of urine.

As in other tests for hepatic disease, impairment of this function is manifest much more strikingly with acute diffuse inflammatory lesions than with chronic, focal or degenerative lesions.

In most of the cases included in this group repeated estimations of urinary urobilinogen were performed. The single value given is in each instance the most representative. The results of this study are presented in table 1. In 2 cases of abscess of the liver there was marked elevation of urinary urobilinogen. In each the suppurative process

TABLE 1—*Estimations of Urobilinogen in the Detection of Hepatic Dysfunction*

Case No	Patient	Diagnosis	Urobilinogen, Mg per 100 Ce of Urine	Bile in Urine	Urobilinogen, Mg per 100 Gm of Stool	Icterus Index
1	O O	Abscess of liver	29.25	+	-	17.6
2	O A G	Abscess of liver	32.8	+++	-	20.0
3	J H	Portal cirrhosis	9.3	+	80.0	13.3
4	W D F	Portal cirrhosis	9.0	++	-	23.5
5	H E H	Portal cirrhosis	20.4	++	53.2	23.7
6	M S	Portal cirrhosis	8.5	+	226.0	13.0
7	A S	Cholecystitis and hepatitis	26.6	++	83.7	-
8	L T M	Cholecystitis and hepatitis	16.2	++	-	24.0
9	O R T	Cholecystitis and hepatitis	16.1	+++	99.4	31.4
10	M T G	Lobar pneumonia	11.8	++	-	10.7
11	E C B	Lobar pneumonia	14.8	++	-	-
12	A B	Lobar pneumonia	31.0	++	-	-
13	S S	Bronchiectasis, severe	36.8	++	-	-
14	M D	Ether anesthesia, brain tumor	11.9	+	-	-
15	A L S	Ether anesthesia, tonsillectomy	7.4	+	-	-
16	J T W	Ethylene anesthesia, perianal abscess	14.8	++	-	-
17	J T B	Bile duct carcinoma of liver	No increase	Absent	-	-
18	A B H	Secondary carcinoma from ovary	7.83	+	-	17.6
19	P S	Secondary carcinoma from stomach	No increase	Absent	193.0	-

was generalized. In all 6 cases of portal cirrhosis urobilinogenuria was evident in the pathologic range. Two of these cases, in which the condition was accompanied by severe jaundice, are listed in the second group. In 3 cases of acute or subacute cholecystitis increases of urinary urobilinogen were demonstrated. In 10 cases of cholecystitis not included in the table no increase of urobilinogen was noted. Graham<sup>10</sup> recognized the presence of hepatitis in association with disease of the gallbladder and stressed the necessity of evaluating the state of hepatic function prior to operations on the biliary tract. Estimations of urinary urobilinogen probably furnish the most satisfactory means of obtaining this information. In 3 cases of lobar pneumonia and in 1 of severe bronchiectasis increased urinary urobilinogen was observed. In 3 cases

<sup>10</sup> Graham, E. A. Hepatitis. A Constant Accompaniment of Cholecystitis, Surg., Gynec. & Obst. 26: 521 (May) 1918.

studies were made after administration of general anesthesia. In 2 of these significant increases of urinary urobilinogen were observed. In the third the urinary urobilinogen concentration of 7.4 mg per hundred cubic centimeters, although just below the upper limit of normal values (8 mg per hundred cubic centimeters), probably should be regarded as significant, since it was accompanied by the presence of bile pigment in the urine. In the 1 case of primary carcinoma of the liver which was observed there was no elevation of the urinary urobilinogen. Operation on the abdomen and biopsy revealed a small carcinoma of the bile ducts situated on the anterior surface of the right lobe of the liver. The small size of this tumor undoubtedly accounted for its failure to cause pathologic urobilinogenuria. In 2 cases of secondary carcinoma of the liver urobilinogen values were in the normal range, although in 1 of them the urobilinogen content of the urine was at the extreme upper limit of normal and the urine contained small amounts of bile pigment.

By daily estimations of urinary urobilinogen in the group of cases just described it was possible to obtain much information regarding the progress of the hepatic lesion.

It was observed with considerable interest that on every occasion in which urinary urobilinogen was increased above the normal range there was also a detectable amount of bile pigment in the urine. In most instances the quantities of bile pigment were not great enough to permit detection by ordinary means but were sufficient to give unquestionably positive results with the method of testing described in the first article of this series. In the cases in which determinations of the icterus index were available there was observed in each instance an elevation in the degree of icterus, usually into the subclinical range. Determinations of fecal urobilinogen, when performed, tended to give values in the lower extreme of the normal range.

#### B ESTIMATIONS OF UROBILINOGEN IN THE DIFFERENTIAL DIAGNOSIS OF JAUNDICE

In consideration of any patient with obvious clinical jaundice of moderate or severe degree, one may assume that sufficient hepatic damage is present to cause pathologic urobilinogenuria. If, however, the bile passages are occluded, no increases of urinary urobilinogen will occur because of failure of bile to reach the duodenum. Therefore with obviously jaundiced patients the principal role of determinations of fecal and urinary urobilinogen is to aid in the differential diagnosis of jaundice rather than in the detection of hepatic dysfunction. Jaundice arising from disease of the liver is ordinarily associated with increases of urobilinogen in the urine. Jaundice arising from complete

obstruction of the extrahepatic biliary passages, as is usually the case with neoplastic obstructions, is accompanied by disappearance of urobilinogen from stool and urine. In jaundice caused by partial obstruction of the bile ducts, as with obstruction due to stone, fecal urobilinogen is decreased but rarely completely absent. In such cases urinary urobilinogen is usually decreased, but it may be increased if the obstruction is slight and is accompanied by considerable hepatic damage.

My series consists of 15 cases, including 5 cases of acute intrahepatic jaundice, 2 of chronic intrahepatic jaundice and 8 of jaundice due to obstruction of the extrahepatic biliary passages, in 5 of which the cause was neoplasm. The results of this study are presented in table 2.

In acute diffuse inflammations of the hepatic parenchyma, as typified by the so-called catarrhal jaundice, there is ordinarily a preliminary

TABLE 2—*Estimations of Urobilinogen in the Differential Diagnosis of Jaundice*

Case No	Patient	Diagnosis	Urobilinogen, Mg per 100 Cc of Urine	Bile in Urine	Urobilinogen, Mg per 100 Gm of Stool	Icterus Index
20	F N	Acute diffuse hepatitis	21.0	++++	205.0	211.0
21	L O M	Acute diffuse hepatitis	13.3	+++	77.2	83.0
22	J D J	Acute diffuse hepatitis	13.6	+++	92.3	104.0
23	J L	Arsphenamine hepatitis	14.3	++++	71.6	172.0
24	R D M	Acute diffuse hepatitis	16.2	++++	75.2	91.0
25	B E	Portal cirrhosis	40.0	+++	86.9	67.0
26	T H	Portal cirrhosis	36.0	+++	185.0	73.0
27	T E	Carcinoma of head of pancreas	No increase	++++	Absent	161.0
28	O A O	Carcinoma of head of pancreas	No increase	+++	Absent	119.0
29	B K	Carcinoma of head of pancreas	No increase	+++	Absent	54.0
30	C D	Carcinoma of head of pancreas	No increase	++++	Absent	67.0
31	O I L	Carcinoma of head of pancreas	No increase	++++	Absent	111.0
32	R A O	Stone in common bile duct	No increase	+++	63.0	58.5
33	S M S	Stricture of common bile duct	No increase	++	40.0	70.0
34	S L N	Stricture of common bile duct	No increase	++++	53.0	133.0

rise of the level of urinary urobilinogen into the pathologic range. At the height of the disease complete intrahepatic obstruction commonly develops, so that urobilinogen disappears from the urine and stool. This obstructive stage is transient, usually being of three or four days' duration, during which time the icterus index attains its highest level. This phenomenon has been observed by Wallace and Diamond,<sup>3</sup> Piersol and Rothman,<sup>4</sup> Watson,<sup>8</sup> Rosenberg<sup>5</sup> and White.<sup>6</sup> According to their reports, none of these writers has known the obstructive period to exceed seven days. After the spontaneous relief of intrahepatic obstruction, urobilinogen reappears in the urine in greatly increased amounts, which diminish slowly as the hepatic inflammation and jaundice subside.

In my series 5 cases of acute intrahepatic jaundice were studied. In 1 of these jaundice was the result of arsphenamine hepatitis (case 23). In all cases of this group, with 1 exception (case 22), there was observed at the height of the jaundice a period of three to five days during which no urobilinogen could be detected in stool or urine. Urobilinogen

then reappeared first in the stool, and shortly thereafter large increases of urobilinogen were noted in the urine. After the spontaneous relief of intrahepatic obstruction jaundice subsided promptly in each instance, and urinary urobilinogen slowly returned to normal levels.

Five cases of neoplastic obstruction of the common bile duct were studied. It has been noted by Wilbur and Addis,<sup>7</sup> Wallace and Diamond,<sup>8</sup> Watson,<sup>8a</sup> Rosenberg<sup>6</sup> and White<sup>6</sup> that neoplastic obstruction of the common bile duct is practically always complete, whereas obstructions due to stone are rarely so. These authors found that the persistent absence of urobilinogen from the stool and urine which occurs in most instances of neoplastic obstruction serves to differentiate jaundice arising in this fashion from jaundice produced by stone in the common duct. In cases of neoplastic obstruction of the common bile duct, jaundice is usually so intense and the staining of tissue so diffuse that small amounts of bile may reach the intestine from its bile-stained mucosa. Traces of urobilinogen arising from this source can be detected in the stool by

TABLE 3—*Estimations of Urobilinogen as a Measure of Erythrocytic Destruction*

Case No	Patient	Diagnosis	Urobilinogen, Mg per 100 Cc of Urine	Bile in Urine	Urobilinogen, Mg per 100 Gm of Stool	Icterus Index
35	M C	Congenital hemolytic anemia	28.0	++	2,625.0	26.6
36	A T	Congenital hemolytic anemia	No increase	Absent	675.0	32.6
37	G S	Perniciou anemia	No increase	Absent	860.0	16.0
38	G K	Malaria	12.0	+	634.0	17.0
39	F A R	Anemia following sulfanilamide therapy	59.2	+++	1,133.0	35.0
40	G H S	Aplastic anemia	No increase	Absent	56.7	8.0

Watson's method. With my method, however, the amount of urobilinogen formed is insufficient to yield a positive result. In case of jaundice due to stone, some urobilinogen can almost invariably be demonstrated in the stool or urine at some time.

In each of the 5 cases in my series it was possible to make a diagnosis of neoplastic obstruction of the common bile duct by observing persistent absence of urobilinogen from the stool over a period of at least seven days. Urobilinogen reappeared in the stool in normal amounts and in the urine in greatly increased quantities after surgical establishment of a new channel for passage of bile into the intestine.

Three cases of partial obstruction of the common duct were observed. In 1 case obstruction was caused by stricture which followed exploration of the common duct (case 33). In case 34 severe intermittent jaundice of several weeks' duration resulted from an anomalous vessel which crossed and occluded the common bile duct, the jaundice subsided promptly after ligation of the vessel. In case 32 the obstruction was caused by a stone in the common bile duct. After relief of the

obstruction increased amounts of urobilinogen appeared in the urine, gradually diminishing as the patient improved

It has previously been stated that any condition which causes obvious clinical jaundice of moderate or severe degree is associated with sufficient hepatic damage to cause pathologic urobilinogenuria, if bile is reaching the duodenum. For example, with neoplastic obstruction of the common bile duct the associated biliary cirrhosis is sufficient to cause increases of urinary urobilinogen were it not for the fact that the obstruction prevents bile from reaching the intestine. One may therefore expect increases of urobilinogen to follow surgical or spontaneous relief of complete or partial obstructions of the common duct.

In employing determinations of urobilinogen in the differential diagnosis of jaundice it is essential that repeated analyses be made for several days. The urobilinogen findings during the obstructive phase of acute intrahepatic jaundice are similar to those associated with neoplastic obstruction of the common bile duct, and diagnosis of the latter can be made with certainty only when it has been demonstrated that the obstruction has existed for at least a week. By repeated estimations in cases of acute intrahepatic jaundice it is often possible to predict the subsidence of jaundice before it is manifest clinically or is indicated by a fall in the icterus index.

#### C ESTIMATIONS OF UROBILINOGEN AS A MEASURE OF DESTRUCTION OF RED CELLS

Estimation of urobilinogen in the measurement of destruction of red cells is largely confined to the stool. In cases of uncomplicated hemolytic disease the liver is capable of disposing of large excesses of bilirubin, so that greatly accelerated erythrocytic destruction can occur without associated increase in urinary urobilinogen. It is frequently observed, however, that in cases of severe hemolytic disease there is considerable increase of urobilinogen in the urine. This has been variously explained as due to complicating hepatic damage or to simple overflow of excessive urobilinogen through the liver. Watson expressed himself in favor of the former view.<sup>8d</sup>

The 6 cases in this group consist of 5 instances of anemia of increased destruction of red cells and 1 of decreased production. In 2 cases of congenital hemolytic anemia, 1 case of malaria, 1 case of pernicious anemia and 1 case of anemia which followed sulfanilamide therapy there were increases of fecal urobilinogen above the normal range. In 1 case of aplastic anemia the urobilinogen of the stool was below the normal range.

In 3 cases of hemolytic disease (cases 35, 36 and 38) increase of urinary urobilinogen was also noted. In each instance in which this increase was observed bile pigment was also detected in the urine.



## COMMENT

In the present study the series of cases, although small, demonstrates conclusively that information of value may be obtained from the examination of single specimens of stool and urine according to the method described

By this method it is possible to detect hepatic damage and to follow its course. Differentiation can be made between jaundice of intra-hepatic origin and that arising from obstruction to the extrahepatic biliary passages. The importance of this differentiation in recognition of conditions which require surgical intervention is obvious. Neoplastic obstruction of the common bile duct can usually be differentiated from other causes of obstruction by the persistent absence of urobilinogen in the stool. The rate of destruction of red cells can be estimated, and differentiation between anemias of increased destruction and those of decreased production is aided. The method affords a means of detecting significant hepatic damage which accompanies acute or subacute disease of the gallbladder.

In working with the stools of patients with complete and partial occlusion of the bile ducts it has been forcibly impressed on me that little idea as to the amount of bile pigment derivatives which the stool contains can be obtained from observation of its color. Completely acholic stools frequently have considerable color, derived either from ingested material or from blood. Chemical analysis is essential if any accurate idea is desired regarding the amount of pigment in a stool.

Utilization of a sensitive test for bile pigment has demonstrated that significant increases of urinary urobilinogen are always accompanied by the presence of detectable quantities of bile pigment in the urine.

Rich<sup>11</sup> made a broad subdivision of jaundice into the retentive and the regurgitant type. The former type arises as a result of increased destruction of red cells with retention of excesses of bile pigment in the blood stream and is characterized by absence of bile pigment from the urine. The regurgitant type arises from regurgitation of whole bile into the blood stream and is produced by disease of the liver or obstruction of the bile passages. The bile pigment entering the blood in such cases is more diffusible and is capable of passing the kidney, so that it appears in the urine.

Rich suggested, however, that the ability of the normal liver to dispose of large excesses of bile pigment is so great that it may even be impossible for clinical jaundice to arise solely as a result of increased destruction of red cells, he stated that the appearance of jaundice in such an instance points to hepatic damage and indicates that a regurgi-

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11 Rich, A. R. Pathogenesis of the Forms of Jaundice, *Bull. Johns Hopkins Hosp.* 47:338 (Dec.) 1930.

tant as well as a retentive component of the jaundice has developed. If these theoretic concepts are true, the appearance of obvious jaundice and of urobilinogenuria should be accompanied by the appearance of bile pigment in the urine, since this finding is characteristic of regurgitant jaundice. By the sensitive method employed in my series bile pigment was demonstrated in the urine of every patient who had pathologic urobilinogenuria.

Thus the finding of bile pigment and urobilinogen associated in the urine in certain cases of hemolytic jaundice lends support both to the ideas of Rich regarding the pathogenesis of the various forms of jaundice and to Watson's belief that pathologic urobilinogenuria occurs in hemolytic processes only when there is complicating damage to the liver.

It is no doubt true that in cases of borderline hepatic damage or during slight deviations from the normal balance between production and destruction of red cells additional information may be gained from the use of more delicate methods for the estimation of urobilinogen or from the analysis of specimens collected over longer periods. For general diagnostic use, however, the method described has proved highly satisfactory.

#### SUMMARY AND CONCLUSIONS

The method previously described for determinations of urobilinogen in stool and urine is applicable to routine clinical use.

Valuable clinical information can be obtained from examination of single specimens of urine and stool.

Such estimations of urobilinogen are of value in detecting and following the progress of hepatic damage. This is especially true in cases of abscess of the liver, portal cirrhosis or significant hepatic damage accompanying acute and subacute disease of the gallbladder.

Determinations of urobilinogen are of value in the differential diagnosis of jaundice. Differentiation can usually be made between jaundice of intrahepatic origin and that arising from obstruction of the extrahepatic biliary passages. In the latter condition it is usually possible, by means of studies on urobilinogen, to distinguish between obstructions of the bile passages due to neoplasm and obstructions arising from other causes.

Determinations of urobilinogen in the stool by my method afford an index of the rate of erythrocytic destruction and aid in the differentiation between anemias of increased destruction and anemias of decreased production.

Increases of urinary urobilinogen are consistently associated with the presence of bile pigment in the urine, which indicates that pathologic urobilinogenuria does not occur from excessive destruction of red cells unless there is concomitant hepatic damage.

# PANCREATIC CARCINOMA

## A REVIEW OF THIRTY-FOUR AUTOPSIES

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Carcinoma is the most common tumor of the pancreas. Its incidence has been cited as from 1.76 to 2 per cent in cases of cancer in which autopsy was done<sup>1</sup>. The types of carcinoma vary considerably in histologic appearance and manner of growth. Three main categories are recognized as representing duct, acinar and "islet" structures<sup>2</sup>. Rarer types, such as mucoid, colloid or squamous (duct) forms, were not seen in this series.

As with cancer situated elsewhere, the causes are unknown. In view of the complex origin of the mature pancreas, which involves anatomic and functional fusion of two separate (dorsal and ventral) duct systems (Wirsung and Santorini), the possibility of developmental errors may be of some importance. This supposition is further supported by the frequency with which carcinoma occurs in the head of the pancreas and the preponderance of the duct type. To this evidence must be added the unstable, constantly regressing and reforming structure of the pancreas, with recurrent waves of loss and hyperplasia of tissue<sup>3</sup>. But all such considerations remain at present speculative as regards development of cancer.

Of particular interest in these cases are associated lesions. Thus, anatomic evidence of chronic irritation is commonly observed in these parts of the pancreas uninvolved by carcinoma. This takes the form of an increase in stroma, either local, about the tumor, or more diffuse, throughout the whole gland. It is probable that this is, in at least a number of cases, an effect produced by the presence of tumor in the

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From the Pathological Institute, McGill University, Prof. Horst Oertel, Director.

1 Ewing, J. *Neoplastic Diseases*, ed. 3, Philadelphia, W. B. Saunders Company, 1928, p. 746.

2 In this communication the term "islet," as applied to cells or structures, denotes simply morphologic resemblance to islet cells of the pancreas; it does not refer to a definite or distinct entity. Indeed, the term in these cases cannot always be strictly applied as indicating types distinct from duct forms.

3 Oertel, H., and Anderson, C. M. *Regressive and Progressive Changes in the Pancreas*, Scientific Reports, series B, no. 1, Royal Victoria Hospital, Montreal, 1916, p. 163.

organ and not a previously existing lesion or factor conducive to the development of carcinoma. It is not uncommon to note several independent tumor masses in a single organ.

When the main duct has been obstructed by a tumor, small cystic dilatations, hyperplasia and neoplasia are occasionally observed in the ducts proximal to the obstruction. Carcinoma has been observed arising in or about the wall of a larger, previously formed pancreatic cyst.

In the present series of 34 cases of primary cancer of the pancreas in which autopsy was done at the McGill Pathological Institute over a period of twenty years, 26 of the patients were men and 8 women, a ratio of 3.25:1. The age distribution was as follows. In 2 cases the condition occurred in the fourth decade of life, in 7, in the fifth, in 10 each, in the sixth and seventh, in 4, in the eighth, and in 1, in the ninth.

#### GROSS PATHOLOGIC EXAMINATION

*Distribution of the Tumors*—In 15 cases the head alone was involved by a single tumor mass except in 1 instance, in which there were several small nodules confined to the head. The whole pancreatic gland was studded with tumor tissue in 11 cases. In 8 of these there were a larger mass in the head and smaller nodules scattered throughout the body and the tail. In 2 instances the entire gland was replaced by the tumor, so that no normal portions of pancreatic tissue were identified. In 1 case the whole gland was diffusely involved by smaller foci of tumor growth. The head and body together were the site of tumor formation in 3 cases. Two of these growths were single large masses, and the third was composed of multiple tumor nodules. The body and tail were similarly involved in 3 cases, in 2 of these the tumor was a single large mass and in 1 it was composed of multiple nodules. The body alone was involved in 2 instances by a single mass of tumor tissue.

*Size, Shape and Consistency*—The size of the primary tumors was variable. The largest measurements of single masses ranged from 1.5 to 11.5 cm. Multiple tumor masses varied from the size of a pinhead to 3 cm in the greatest dimension. In some instances microscopic foci of cancer formation were later detected.

Size and shape bore no relation to origin of tissue. Some tumors were large, ovoid and well demarcated, others were large and fused to the surrounding parenchyma. Some appeared as retracted, firm, scarified areas. Smaller nodules were frequently apparent only on palpation. Some tumors were centrally placed, while others bulged from the surface of the organ.

In general these tumors were firm and hard. A few felt soft or cystic. Cut surfaces were usually a pale homogeneous yellowish gray or white. Some contained softer areas, also seen in their metastases,

from which could be scraped a milky substance. Others had small areas of hemorrhage and necrosis. In 1 case the tumor arose in the wall of a large pancreatic cyst.

*Pancreatic and Bile Ducts*—When blockage of the pancreatic duct had occurred by pressure or invasion of the tumor in the head, the proximal portion was usually tortuous and dilated with a milky or watery fluid. Many small cystic dilatations were seen throughout the length of such ducts. Frequently the pancreatic tissue proximal to the obstruction appeared atrophied or collapsed or felt soft. Pancreatic calculi were not noted in any of the cases.

The common bile duct was obstructed in 12 and compressed in 8 instances. In these cases 6 tumors were in the head, 10 involved the whole gland, and 1 occurred in the body with extension into the head. In 3 cases lymph nodes in the gastrohepatic ligament caused pressure on the common bile duct. Stone in the common duct was observed in only 1 case, and in this it was associated with obstruction by a lymph node.

*Extensions and Metastases*—There appeared a definite tendency in these tumors first to adhere to adjacent structures and then to infiltrate them. Coaptation was brought about by enlargement of the part of the organ involved by tumor or by direct infiltration and contraction of intervening tissues. This tendency to stimulate formation of abundant stroma and connective tissue within the tumor, the organ and the surrounding tissues has been spoken of as a desmoplastic property of pancreatic carcinoma.

*Gastrointestinal Extension* Local extensions, excluding involvement of lymph nodes, occurred in 18 cases. The pylorus of the stomach was adherent in 8 instances. In 3 of these cases there was gastric ulcer with metastatic invasion, and in 1 the wall of the stomach was invaded, the mucosa being left intact. In 2 other cases gastric ulceration occurred without metastases or adhesion. The duodenum was adherent in 10 cases. In 3 of these there was duodenal ulceration with carcinomatous invasion. In 6 cases the tumor invaded the duodenal wall, leaving the mucosa intact, and in 1 case there was simple adhesion to the tumor mass. In the cases in which there was carcinomatous ulceration of the gastrointestinal tract, the gross appearance of raised thickened edges and radiating rugae suggested previously existing peptic ulceration with secondary carcinomatous invasion. The tumor was adherent to the transverse colon in 4 instances and had invaded its outer coats in 1 case. The descending colon was invaded by peritoneal metastases in 2 cases, in 1 of which the bowel was partially obstructed without ulcerating.

*Metastases to Peritoneum* Peritoneal seeding occurred in 8 cases. In 2 of these the nodules were localized to the region about the tumor, while in the remainder multiple and single nodules were observed in

more remote parts of the abdomen, including the cul-de-sac (3 cases) Ascites was found in 3 of the 8 cases

**Metastases to Lymph Nodes** This involvement was frequent Regional nodes (gastrohepatic and pancreatic) contained metastases in 28 instances Retroperitoneal lymph nodes about the abdominal aorta were involved in 15 cases Extension into the nodes of the mesentery occurred in 11 cases, and metastasis to the mediastinal and peribronchial lymph nodes was observed in 8 The supraclavicular nodes were involved in 3 instances, in 1 on the right, in 1 on the left and in 1 bilaterally, and the inguinal nodes in 4 cases, in all on the right

TABLE 1—*Distribution of Metastases in Thirty-Four Cases of Primary Carcinoma of the Pancreas\**

Organ	No. of Cases
Regional lymph nodes	28
Liver	25
Para aortic abdominal lymph nodes	15
Mesenteric lymph nodes	11
Lungs	10
Mediastinal lymph nodes	8
Peritoneum	8
Duodenum	8
Adrenals	7
Skeleton	7
Kidneys	6
Omentum	4
Spleen	4
Inguinal lymph nodes	3
Stomach	3
Intestines	3
Supraclavicular lymph nodes	3
Central nervous system	3
Thyroid	2
Subcutaneous tissue	2
Skeletal muscle	2
Gallbladder	2
Pleura	2
Myocardium	1
Esophagus	1
Pericardium	1

\* In 3 cases no metastases were observed

**Metastases to Liver** The liver exhibited metastases in 25 of the 34 cases of pancreatic carcinoma With 1,300 to 1,800 Gm as a normal range of hepatic weight and with allowance for variation in the size of individual subjects, the weight of the liver was increased in 12, decreased in 7 and normal in 6 of the 25 cases In this connection the distance of the hepatic border below the costal margin was not consistent with the weight of the organ In several instances an apparently enlarged liver, with its anterior border well below the costal margin, actually weighed less than normal This may have been due to traction on the gastrohepatic ligament, brought about by adhesive and contractive processes in the region of the tumor and its local extensions, or to actual ptosis

of the organ The majority of livers containing metastases were smooth and firm Metastases were usually small and multiple and did not bulge the capsule Ten of the 25 patients with hepatic metastases showed no jaundice, while jaundice occurred in 5 in the series without metastases to the liver

*Jaundice*—Of the 20 patients exhibiting jaundice, 15 had obstruction of the common bile duct by compression or invasion of the tumor, 3 had compression of the duct by enlarged nodes in the gastrohepatic ligament, and 2 had patent ducts Both of the latter exhibited metastases in the liver, 1 of them had thrombosis of the portal vein, and the other, thrombosis of the inferior vena cava In no other case did thrombosis occur in vessels directly related to the hepatic circulation It seems therefore that thrombosis in the afferent or efferent veins of the liver is a factor in the production of jaundice Metastases to the liver apparently play a minor part in the production of jaundice, except when main hepatic ducts become obstructed by metastases near the hilus or when there is massive replacement of liver by tumor tissue Both of these events are rare

*Effects of Biliary Obstruction*—All of the 18 patients with obstruction of the common bile duct showed dilatation of the intrahepatic and extrahepatic biliary tree of varying degree Similarly, the gallbladder was seen to be dilated either at operation or post mortem Three patients had associated productive cholecystitis, 2 with cholelithiasis In all cases the gallbladder and duct bile were of normal color and consistency, except in a case of gallstones in which the thickened gallbladder was tensely dilated with pale mucoid material

Evidence obtained from clinical, operative and postmortem examinations suggested in most instances the following sequence of events with respect to hepatic enlargement With the onset of biliary obstruction the gallbladder and the extrahepatic and intrahepatic bile ducts dilate, and the liver gradually enlarges In the course of time progressive atrophy of the hepatic parenchyma supervenes This sequence of events seemed well illustrated in a case in which the liver, with metastases, weighed at autopsy only 750 Gm, although it had been palpably enlarged during life and was noted as "enlarged" during operation (cholecystogastrostomy), three weeks before death Generally, however, when metastases were numerous the liver remained enlarged (over 2,000 Gm in 8 cases)

*Ascites*—Ascites was present in 8 cases Peritoneal metastases associated with ascites occurred in 3 instances Other reasons for ascites appeared to be partial obstruction of the venous return, portal and caval, by enlargement of lymph nodes, hepatic metastases and portal thrombosis In 1 case definite peri-insular cirrhosis of the liver

was associated with ascites. In another case there was chylous ascites from massive tumor invasion of lymph nodes in the region of the diaphragmatic crura. The ascitic fluid was usually pale yellow and cloudy and occasionally blood tinged.

*Edema*—Edema of the lower extremities occurred with ascites in 5 instances. Swelling of the feet and legs, unilateral or bilateral, occurred independently of ascites in 5 cases. In 3 of these thrombosis of the femoral or iliac veins was demonstrated, with extension into the inferior vena cava in 2 instances. Metastases to the right inguinal lymph nodes were responsible in 1 case and peritoneal metastases in the left lower quadrant in another.

*Metastases to Skeletal and Central Nervous Systems*—Skeletal metastases occurred in 7 cases. The spine and ribs were involved in 3 cases, the clavicle in 2 and the skull, sternum, scapula, ilium, sacrum and femur in 1 instance each. Growths in the vertebrae caused pressure on the cord. The central nervous system showed metastases in 3 instances. The brain and the dura were involved in 2 cases and the longitudinal sinus and the spinal cord in 1.

#### MICROSCOPIC EXAMINATION OF PANCREAS

*Pancreatic Invasion*—The manner of expansion and invasion of these tumors within the pancreas deserves mention because of the possibility of mistaken diagnosis due to bizarre formations and degrees of disintegration and collapse in the tissue adjacent to the tumor. Such sections revealed an increase of stroma, with varying degrees of collapse of parenchyma and dilatation of intralobular ducts and acini and breaking down of acini and smaller ducts into single or small groups of cells. In these fields there was a distinct tendency for islet cells to remain conspicuous. Thus, typical duct carcinoma or acinar carcinoma will in the cirrhotic environment of the periphery alter the normal structure of ducts and acini to the appearance of new growth, although in reality no actual tumor has overgrown these parts.

The picture produced in individual lobules was not unlike that seen in the proximal portion of the pancreas in some instances in which the main pancreatic duct was obstructed. Complete pathologic obstructions of the duct in the head or body eventually lead through atrophy and collapse to total disappearance of acini and lobular structure, with increase of stroma and prominence of islet tissue about larger dilated ducts in the proximal parts of the gland (fig 1). It appears that local expansion of cancers within the pancreas leads to strangulation or obstruction of the efferent ducts of individual lobules, with resultant loss of acini and proliferation of stroma. This possibility is further supported by the appearance of dilated acini and ducts within lobules in earlier stages of invasion of adjacent tissues.



Sections frequently showed an apparent increase in larger interlobular ducts, which were surrounded by increased stroma, in some instances resembling foci of carcinomatous duct growth. Closer inspection revealed that this growth was only apparent, being the result of atrophy, collapse or total loss of lobules. In some instances, however, in which partial obstruction had evidently persisted longer, there was definite papillary hyperplasia, particularly in larger dilated ducts. In 1



Fig 1—*A*, effect of the tumor on adjacent pancreatic tissue. *B*, result of obstruction of the pancreatic duct. Note the total loss of acini and of the lobular structure and prominent islet tissue about the larger ducts.

instance this had gone on to neoplasia, with the formation of an intra-ductal papillary adenoma in the tail (fig 2).

*Characteristics of Tumors*—Of the 34 tumors, 25 were of the duct, 7 of the acinar and 2 of the islet type of carcinoma. The duct cancers showed an excessive amount of stroma as compared with the other types. These varied slightly, but all exhibited distinct duct formation.

regardless of whether the tendency was to grow in solid or in alveolar fashion. The size of the ducts, the height of the lining epithelium and the tendency to papillary growth were all variable. Cell types ranged from tall columnar to low cuboidal and from pale mucoid to deeper-staining, finely granular cytoplasmic. Thus, cell types and arrangements emulating intralobular, extralobular and main ducts were seen in this group (fig 3)

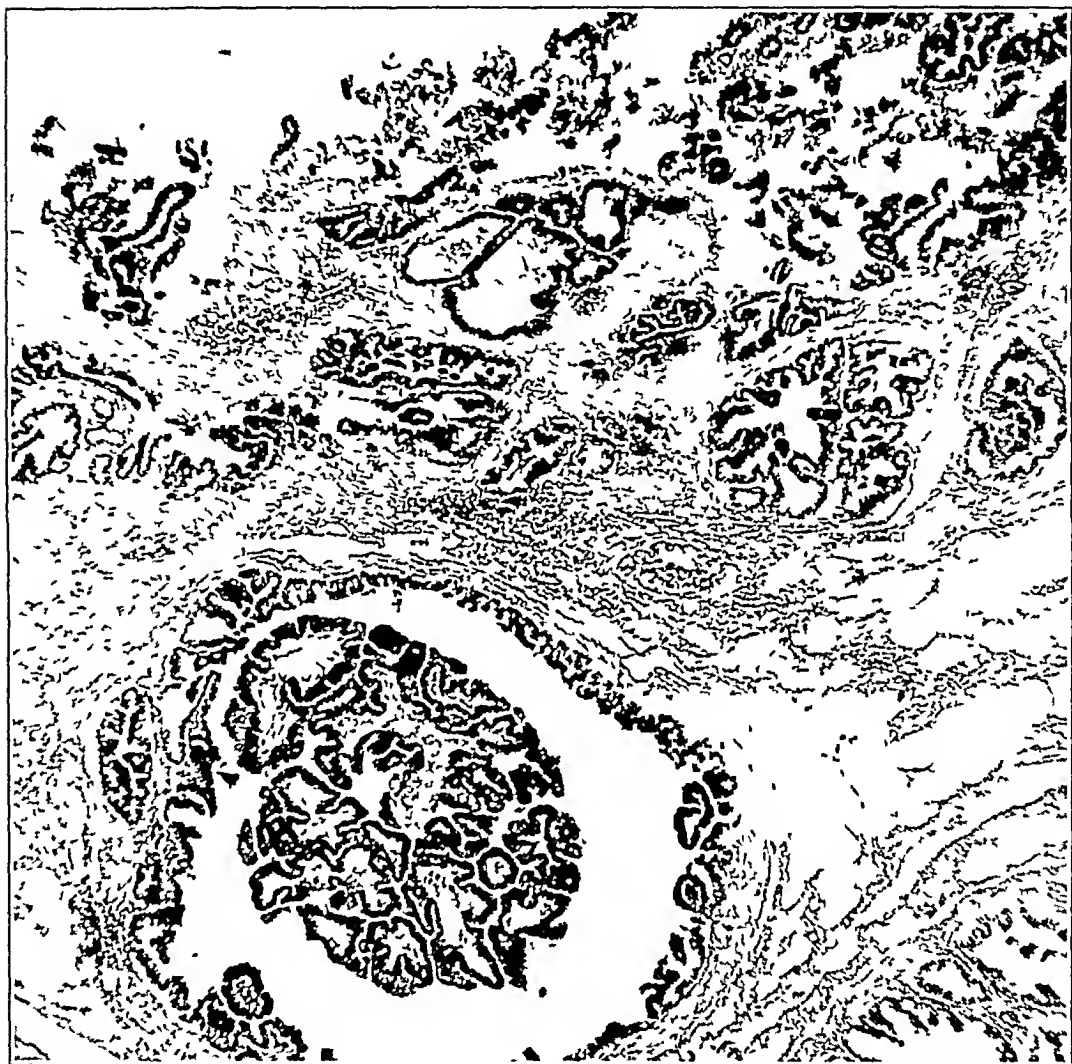


Fig 2—Papillary hyperplasia with obstruction of the main duct. Note the adenoma formation and the collapse of surrounding parenchyma.

The 7 acinar carcinomas all grew as solid masses of cells, with little stroma between cells. Larger cell masses were separated by more definite fibrous cords. These tumors had a distinct, solid diffuse or solid alveolar manner of growth. Only at the periphery of such tumors were ductlike structures suggested in the breaking down lobules. There was a greater tendency to tumor necrosis in this group. Cell types varied more than in the other two varieties of carcinoma. Polyhedral

cells, small round cell types and even elongated, spindle-like shapes were seen (fig 4)

The 2 islet carcinomas showed a distinctive manner of growth closely resembling the islet adenomatous structure. The presence of metastases and local invasive properties, however, indicated the cancerous nature of these tumors. In places they exhibited a tendency to grow in more solid cell masses, and in others a tendency to duct forma-

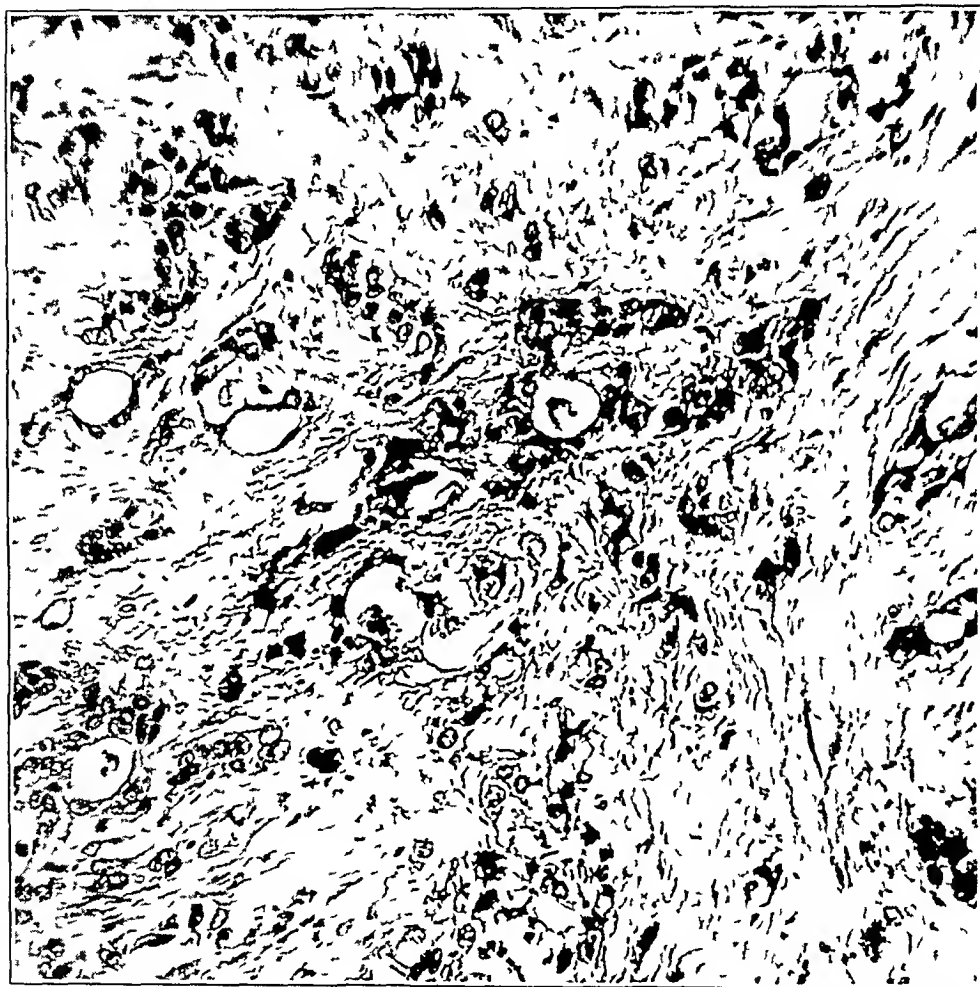


Fig 3—Typical duct carcinoma. Note the abundant sclerotic stroma, the abortive duct formations and the cell masses.

tion was noticeable, but with cell types characteristic of islet tissue. These peculiarities are explicable on the basis of origin of islet tissue from intercalary ducts and centroacinar cells (fig 5).

*Relation of Pancreatic Carcinoma and Blood Sugar*—Determinations of blood sugar were made during the course of the disease in 14 cases (table 2). With the upper normal limit of the level during fasting

as 120 mg per hundred cubic centimeters and the upper normal limit for the postcibal level as 150 mg, in this group of 14 cases there were 8 instances of a raised sugar level, 5 cases of a level within normal limits and 1 instance of a decreased postcibal level. Sugar tolerance tests were made in cases 21 and 32. In the former a normal curve was exhibited, and in the latter a decreased tolerance curve of the prolonged, raised type.

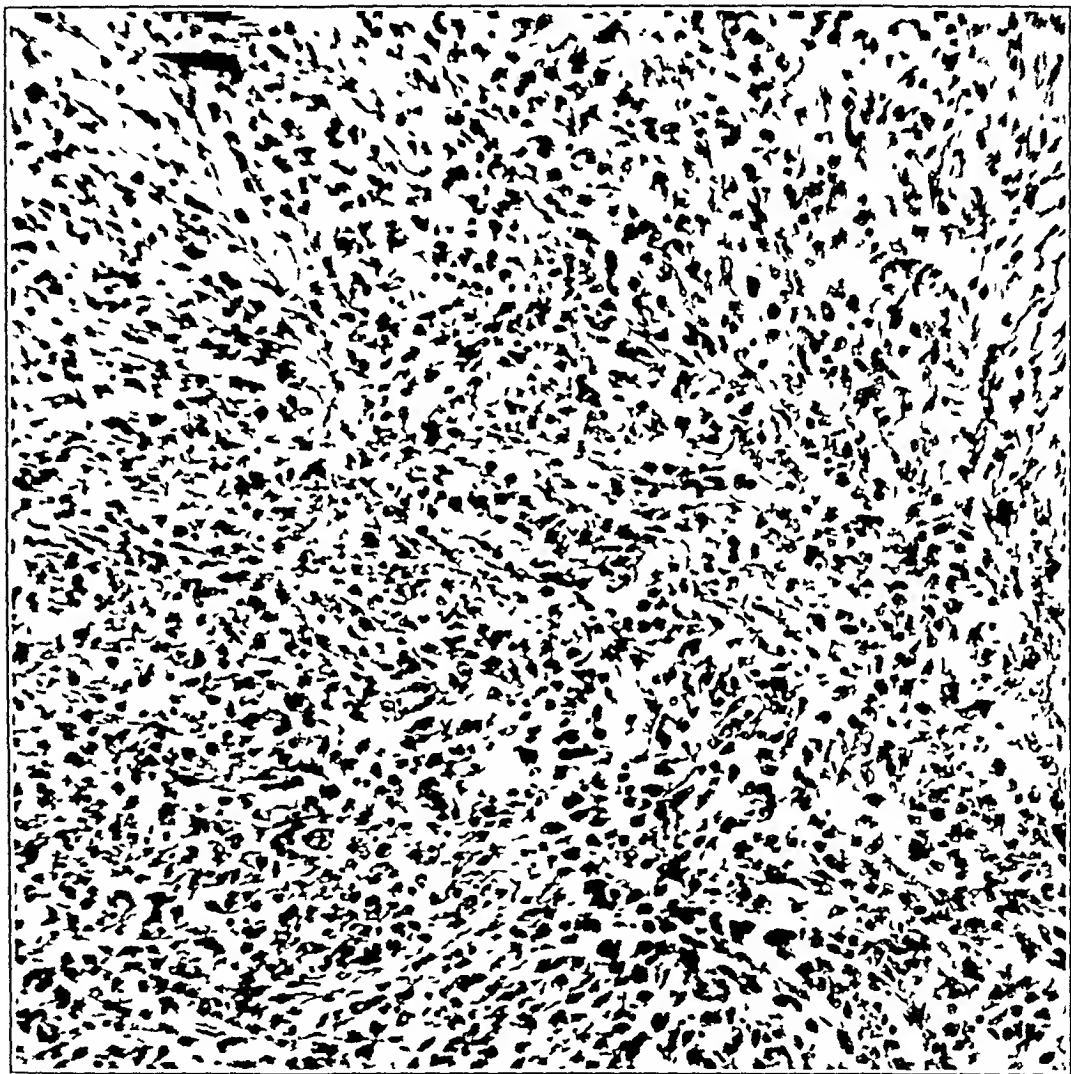


Fig 4—Typical acinar carcinoma, showing pleomorphic cell types and a diffuse manner of growth

No correlation could be established between altered sugar levels and the hepatic weight, metastases to the liver, obstruction of the common bile duct or metastases to other organs known to have a physiologic effect on the blood sugar level. Stains for glycogen granules of the liver (Best's carmine method) revealed that they were decreased and confined to the periphery of the lobules.

The changes in the pancreas showed the most consistent correlation with the blood sugar level. Unfortunately, studies on sugar were not made in the 2 cases of single islet cancer. It appears, however, that both the duct and the acinar type of carcinoma exhibited associated effects on the blood sugar level. Nevertheless, in 5 cases in this group the blood sugar range was normal. It appears therefore that the effect, if any, produced by carcinoma of the pancreas on the blood sugar level

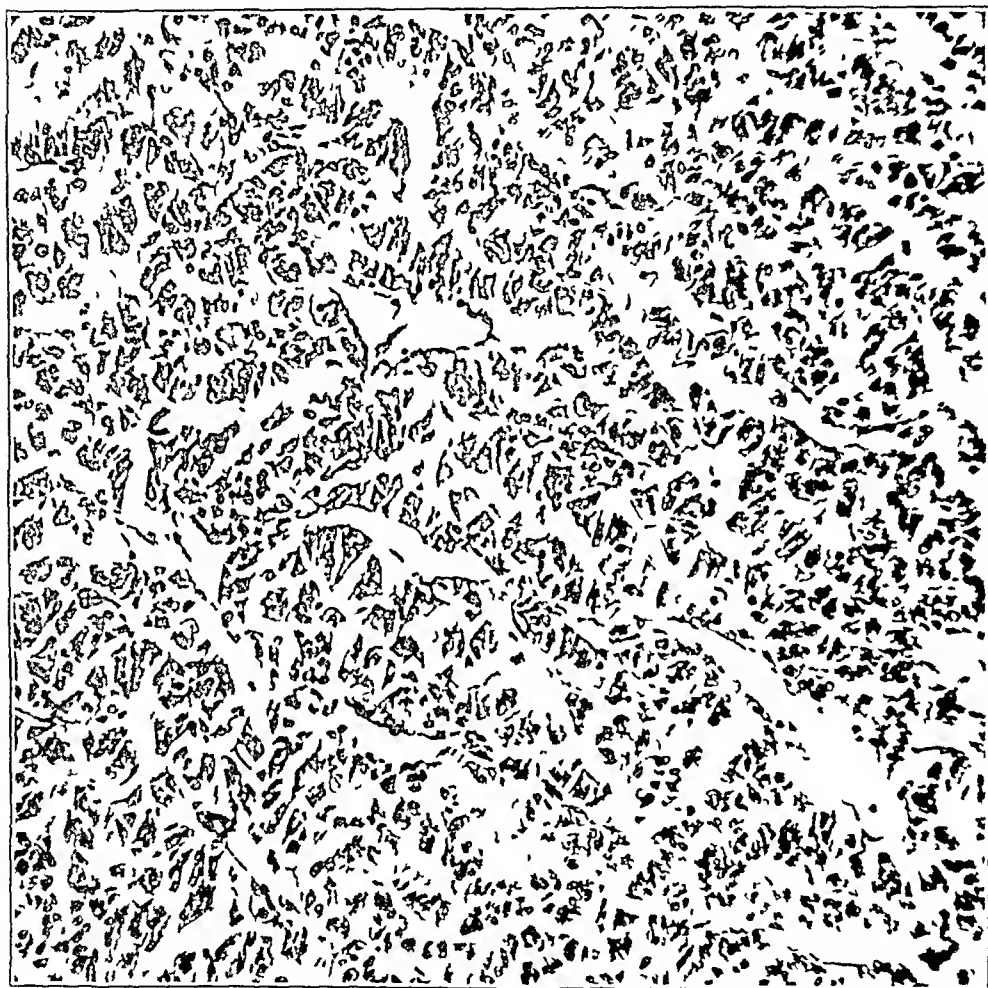


Fig 5—Islet carcinoma, showing cells arranged about vascular spaces

must be due not to the type of tumor but to the effect of the tumor on the rest of the pancreatic gland. When the pancreas has been totally replaced by tumor growth, when massive collapse of pancreatic tissue has occurred proximal to tumor obstruction of the main pancreatic duct or when diffuse fibrosis has led to extensive loss of parenchyma, a disturbance in blood sugar levels is almost uniformly assured.

Sections from the parts of the pancreas which were not involved in actual tumor growth all showed relatively well preserved islet tissue

Various degrees of lobular atrophy and loss of acini and intralobular ducts were noted in all cases in which blood sugar levels were disturbed. In the cases of most severe involvement, in which there occurred the equivalent of ligation of the pancreatic duct, there was total collapse of acini and of the lobular structure, with groups of islands arranged about dilated extralobular ducts. In several cases there appeared diffuse increase in perilobular connective tissue, which in some instances grew diffusely throughout the lobules. In these instances there was associated loss of acinar tissue, and the picture was not unlike that seen in hepatic cirrhosis.

Definite conclusions cannot be drawn, nor can a hypothesis be established, on the basis of the present analysis. That the control of blood sugar levels is not entirely localized in the pancreas is shown by

TABLE 2—*Blood Sugar Levels in 14 Cases of Pancreatic Cancer*

Case No	Site	Size	Type	Blood Sugar, Mg per 100 Cc	
				During Fasting	Post cibal
5	Head	3 cm in diameter	Duct	164*	
6	Head	5 cm in diameter	Duct	119	144
11	Head	5 cm in diameter	Duct	131*	
13	Head, body and tail	Half of head free	Acinar	133*	
17	Body and tail	7 cm in diameter	Duct	372*	369*
21	Head, body and tail	Multiple nodes	Duct	99	141
23	Head	Multiple nodes	Duct	97	136
26	Body and tail	Multiple nodes	Duct	102	185*
28	Body	11 by 5 cm	Acinar	105	163*
30	Head and body	8 by 4 cm	Duct	200*	
32	Head, body and tail	Multiple nodes	Duct	102	174*
33	Head	2 cm in diameter	Duct		147
24	Body	8 cm in diameter	Duct		120
10	Head, body and tail	Multiple nodes	Duct		72

\* Level abnormally high

the effects produced on sugar values by pathologic lesions in the brain, hypophysis cerebri, thyroid and adrenals. One conclusion may be stated, however, with regard to pancreatic carcinoma other than the islet type. As previously mentioned, the type of carcinoma, duct or acinar, is of less importance in relation to blood sugar values than the effect produced by the tumor on the rest of the pancreatic gland. When loss of parenchymatous substance, and acinar structures in particular, has occurred in the pancreas outside the tumor proper, there is a tendency to a raised blood sugar level and lowered sugar tolerance.

#### CLINICAL NOTES

In this group of 34 cases of primary pancreatic carcinoma, the earliest symptoms were related to the primary tumor in 28 instances and to metastases in 6.

The earliest common complaint was epigastric pain in 20 cases. This varied widely, ranging from a dull ache to a sharp colicky pain and from an intermittent to a persistent form. The commonest site for radiation of pain was the right upper quadrant of the abdomen and the lower part of the right thorax anteriorly. Only 5 patients had pain in the back during the course of the disease. Pain related to meals occurred in a few instances, beginning anywhere from fifteen minutes to two hours after food was taken. Four patients had a typical history of peptic ulcer, although no gastrointestinal lesion was demonstrable post mortem.

Clinical symptoms of hypoglycemia were not recorded in this series, even in the 2 cases of the more typical islet types. A feeling of fullness, gaseous eructations and general weakness were early common complaints. Anorexia and loss of weight were prevalent, but usually appeared late. Constipation occurred with greater frequency than diarrhea, particularly in jaundiced patients. No anatomic lesions were observed which directly explained the diarrhea. It is assumed that interference with the normal production and flow of digestive ferments was responsible in these instances. In 1 case the duodenal contents were analyzed, and no pancreatic ferments were demonstrable. The color and consistency of diarrhetic stools were inconstant.

Nausea and occasional vomiting occurred in 11 instances, but as a rule not as an early symptom. However, in a few cases morning nausea did appear early. In 5 patients with these symptoms, gastrointestinal lesions were revealed at autopsy. These consisted of nodular extension of the tumor into the duodenum and stomach and adhesions to the pylorus, duodenum and transverse colon. In some ulceration was associated with metastases.

Gastric analyses were made in 12 cases. In 7 there was no free hydrochloric acid. In only 1 case of this group was a gastric lesion revealed at autopsy, this was an ulcer with metastatic invasion. No correlation could be established between achlorhydria and hepatic weight, metastases to the liver or gross gastrointestinal lesions.

Onset of jaundice without pain occurred in only 3 cases in all of which epigastric pain subsequently appeared. Jaundice occurred in 20 of the 34 cases, in 6 it appeared early, in 5 about midway and in 9 late in the course of the disease. Once established, it persisted in all cases.

Fullness in the upper part of the abdomen, excluding that due to ascites, was frequently observed. Many patients had tenderness with some resistance in the epigastrium and in the right upper quadrant. The liver was palpable in 15 cases, the gallbladder in 7 and the spleen in 3, and masses were felt in other abdominal sites in 2. Clinically the

Bard-Pic syndrome<sup>4</sup> (distention of the gallbladder, absence of hepatic enlargement, jaundice and rapid cachexia) was the exception rather than the rule in early stages. This syndrome was more frequently observed post mortem. Peritoneal metastases were palpated by rectum in 3 instances.

More frequently hypochromic anemia developed late rather than early. The white cell count usually showed slight neutrophilic leukocytosis with relative lymphopenia and monocytosis. Velocities of sedimentation were usually accelerated.

Roentgen examination with barium sulfate given orally or by enema revealed abnormalities in most, but not all, cases in which lesions involving the gastrointestinal tract were demonstrated at autopsy. In other instances, when roentgen studies gave negative findings, the gastrointestinal tract was uniformly normal post mortem. The commonest roentgen finding was gastric delay. A few patients showed irregularities or deformities in the outline of the stomach or duodenum, very few had colonic filling defects in the transverse colon where peritoneal metastases had caused narrowing of the lumen.

The 6 patients whose earliest symptoms were related to metastases uniformly had pain in the legs, hips or arms, sometimes of sciatic nature and usually unilateral. In 3 instances this progressed to sensory or motor paralysis or to both. Metastases to the skeleton were demonstrated in 5 of the 6 cases and to the dura or brain in 3 instances. In 1 patient ulnar paralysis had developed from pressure of lymph nodes in the supraclavicular fossa on the brachial plexus.

There was wide variation in the duration of the disease as measured from the onset of the earliest symptoms until death. In 2 instances complaints began five and seven years, respectively, prior to the patient's demise. In 2 patients the course extended over a period of three years and in 2, over two years. The remaining 28 patients died within a year of onset of symptoms, as follows: Four lived one to two months, 5, two to three months, 4, three to four months, 4, four to five months, 2, five to six months, 1, six to seven months, 5, seven to eight months, and 1 each, nine, ten and eleven months. It is thus seen that the illness may be sudden and acute or gradual and chronic.

#### SUMMARY

Thirty-four autopsies on patients with pancreatic carcinoma are reviewed. The highest incidence occurred in the fifth to the seventh decade, and the condition was present in men 3.25 times as often as in women.

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4 Bard, L., and Pic, A. Contribution a l'étude clinique et anatomopathologique du cancer primitif du pancréas, *Rev. de méd.*, Paris 8 257, 1888.



There were 25 instances of duct carcinoma, 7 of the acinar and 2 of the islet type. Fifteen of the 34 patients had multiple tumor nodules in the pancreas. Obstruction of the pancreatic duct by tumor with collapse and fibrosis of the parenchyma was frequently observed. In a few cases the whole gland was almost completely replaced by carcinoma or was diffusely fibrotic with loss of parenchyma.

The effect on blood sugar levels bore no relation to the type of cancer. In the cases of islet cancer, determinations of sugar levels were not available, but no symptoms of hypoglycemia were recorded. The amount of damage caused by the tumor to the pancreas as a whole did show a relation to sugar levels. There was a general tendency to a raised blood sugar level and lowered sugar tolerance when loss of parenchyma was extensive.

Metastases and other postmortem observations are discussed.

Some clinical observations on pancreatic carcinoma are noted and correlated with changes seen at autopsy.

# THE BREATH-HOLDING TEST

## A SIMPLE STANDARD STIMULUS OF BLOOD PRESSURE

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AND

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The patient with essential hypertension has an excessive physical and emotional response to many different stimuli. The study of these excessive responses, especially of the blood pressure, is of great importance in the early recognition of the disease. The use of a simple standardized stimulus (cold) to study the response of blood pressure in cases of essential hypertension was first reported by Hines and Brown<sup>1</sup> in 1932.

In a previous paper,<sup>2</sup> we reported our own results with 313 cold pressor tests, and in general we have been able to confirm the findings of Hines and Brown. During the past year, we have devised and investigated a new standard test utilizing vasomotor stimulus—the breath-holding test—and the following is a preliminary report of our findings with this test.

### TECHNIC OF THE BREATH-HOLDING TEST

With the subject sitting in a quiet room, the blood pressure is determined at about five minute intervals until a basal level is obtained. This basal level varies with the severity of the hypertensive disease and the degree of relaxation. The length of the rest period varies from twenty minutes to forty-five minutes and is in general much briefer for the subject with normal blood pressure than for the hypertensive patient. If after twenty minutes of rest in a chair the systolic blood pressure of the hypertensive patient does not drop at least 30 mm of mercury, even with advanced disease, it is clear to us from past experience that the patient is still tense and that a basal level has not been reached. In such cases either a longer rest period is used or the test is done with the understanding that a basal

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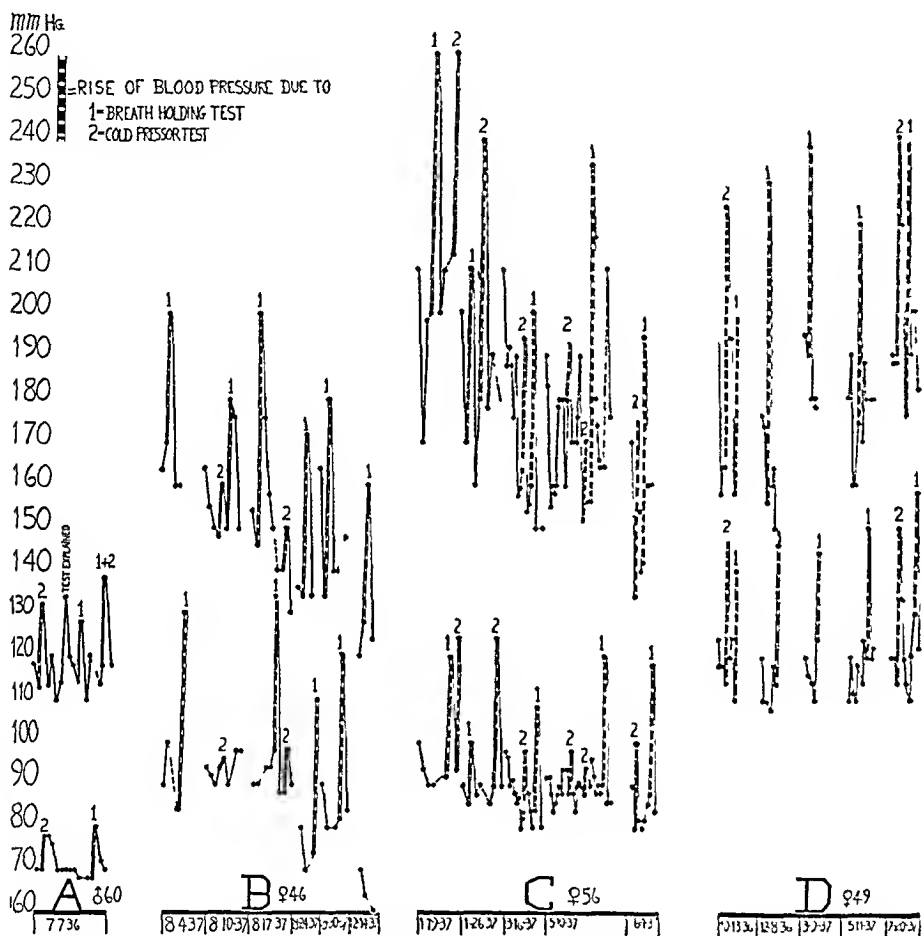
Presented in abstract at a meeting of the New England Heart Association, Boston, March 28, 1938.

From the medical service of the Beth Israel Hospital and the Department of Medicine, Tufts Medical School.

1 Hines, E A, Jr, and Brown, G E. A Standard Stimulus for Measuring Vasomotor Reactions. Its Application in the Study of Hypertension, *Proc Staff Meet, Mayo Clin* 7 332 (June 8) 1932.

2 Ayman, D, and Goldshine, A D. The Cold Pressor Test as a Standard Stimulus of Blood Pressure, *New England J Med* 219 650 (Oct 27) 1938.

level was not obtained. That this is true is invariably borne out by subsequent visits, when the patient has become accustomed to the physician and a much lower basal level of blood pressure is obtained. The chart (C) illustrates the reactions of the blood pressure of a mildly hypertensive patient, whose basal systolic level was 170 mm on the first visit, 160 mm on the second visit and 134 mm on the sixth visit. For subjects with normal blood pressure, a similar rest period is necessary, but usually the basal level is obtained more quickly. When after an adequate fall of blood pressure and at least twenty minutes of rest, we find that



Blood pressure reactions to (1) the breath-holding and (2) the cold pressor test. The upper levels of the chart represent systolic and the lower levels diastolic blood pressure. The numerals at the bottom indicate the dates of individual visits of the same subject. The letters A, B, C and D refer, respectively, to a subject with normal blood pressure, a hyperreactor and 2 subjects with essential hypertension. A complete break in the lines of the chart indicates the end of each visit.

two or three readings of the blood pressure repeated every few minutes are within 10 mm of each other, a basal level is considered to have been reached. (The chart [A] illustrates the basal readings of a typical subject with normal blood pressure.) The technic of the test is then explained to the subject. This explanation in itself is a stimulus to blood pressure in most persons (chart A), so that it must be followed by a few more minutes of rest, till at least the original basal level is again obtained.

The subject is then asked to compress his nostrils suddenly with the fingers of the free hand and simultaneously close the mouth by compressing the lips. He is cautioned in advance and also at the time of the test not to inhale or exhale just prior to the test. Both these points are checked by observation. Actually, the command to close the nose and mouth is given at the observed moment of normal quiet expiration. The subject is told to keep the nose and mouth closed without allowing the slightest amount of air to pass in or out. Further he is advised that the time of holding the breath is to be twenty seconds, and that the final few seconds are usually attended by discomfort. He is also asked to relax his chest and body. During the last five seconds of the breath holding, the subject is strongly urged to resist the impulse to breathe.

At the beginning of the breath holding, the observer pumps up the manometer to the level of the systolic blood pressure and follows the systolic blood pressure during the twenty seconds of the test. If the systolic blood pressure rises, the elevation is greatest during the last half of the breath holding. At exactly the end of the twenty seconds, as determined by the second hand of an ordinary watch, the final systolic reading is noted, the subject is then told to breathe again, and the blood pressure cuff is deflated. The blood pressure returns to or falls slightly below the original basal level within a minute or two. After a few minutes of rest and a return to the basal level, the test is repeated, but this time at the start of the test the cuff is inflated to the level of the diastolic blood pressure and the rise of diastolic blood pressure followed during the test. Although it is possible to determine both systolic and diastolic blood pressure in the one breath-holding period, the time necessary to read both systolic and diastolic pressure will carry the breath holding beyond twenty seconds and make for greater discomfort for the subject and inaccuracy in the diastolic reading. The separate determinations of the rise in the systolic and diastolic blood pressure constitute together one complete breath-holding test.

#### RESULTS OF THE TEST

We have thus far carried out 650 breath-holding tests on 150 ambulatory subjects, 55 of whom had normal blood pressure and 95 of whom had essential hypertension. The average age of both the normal and the hypertensive group was 50 years. Except in rare instances and for particular reasons, the subjects had not used sedatives for at least three days before the test. Our criteria of normal blood pressure were readings well below 145 systolic and 90 diastolic during ordinary visits to the clinic, while blood pressures well above 145 systolic and 90 diastolic constituted among other things the criteria of essential hypertension. Using the original grouping of Hines and Brown, we divided our subjects empirically, first, into those with normal blood pressure and those with essential hypertension (table). We then subdivided the normal group as Hines and Brown did, into a so-called hyporeactor group, in which the rise of systolic or diastolic blood pressure did not exceed 22 mm of mercury, and a hyperreactor group, in which the rise of systolic or diastolic blood pressure exceeded 22 mm of mercury. We have tentatively used a 22 mm rise as the upper limit of a normal hyporeaction, on the basis of the experience of Hines and Brown with the cold test.

The table shows the average rise of the blood pressure in the different groups. Forty-six subjects had normal blood pressure at the time of the test, no clinical evidence of previously elevated blood pressure and a reaction to the breath-holding test of less than a 22 mm rise in either the systolic or the diastolic blood pressure. The mean rise of blood pressure for the group was 11.6 mm of mercury systolic and 11.7 mm of mercury diastolic. This low average rise of blood pressure indicates that most of the subjects had rises much less than the upper limit of 22 mm of mercury. The chart (*A*) represents a typical case.

Nine subjects with normal blood pressure at the start of the test reacted excessively to the test, i. e., with a rise of systolic or diastolic blood pressure of more than 22 mm of mercury. These were called hyperreactors (chart, *B*). The mean rise of systolic blood pressure was 32 mm of mercury, and of diastolic blood pressure, 21 mm of mercury.

Finally, there was the group of 95 subjects with essential hypertension, with varying degrees of hypertension and secondary cardio-

*Results of Six Hundred and Fifty Breath-Holding Tests*

No	Subjects	Classification	Mean Rise in Blood Pressure, Mm	
			Systolic	Diastolic
	Those with normal blood pressure			
46	Hyporeactors (0 to 22 mm of mercury)		11.6	11.7
9	Hyperreactors (22+ mm of mercury)		32.0	21.0
95	Hypertensive subjects	{ Tests made after a good basal level was reached All tests	40.7 31.5	25.4 21.3

vascular changes. There were many in whom the blood pressure on adequate relaxation dropped to normal during many visits (chart, *C*) and a large number in whom a persistent severe hypertension was present (chart, *D*). We did not analyze the reactions according to the different degrees of hypertension or secondary cardiovascular change. We did, however, analyze the reactions of the hypertensive subjects according to whether a satisfactory basal level was obtained before the test. First, in all the hypertensive patients, regardless of the degree of reaction or arrival at a satisfactory basal level, the mean rise of blood pressure was 31.5 mm of mercury systolic and 21.3 mm diastolic. If we omitted those tests in which a basal level was not obtained, as evidenced by later visits and tests, then the mean rise was 40.7 mm of mercury systolic and 25.4 mm diastolic.

The reactions in any given subject in general tend to be reasonably constant in being either of a hyporeactor or of a hyperreactor type. We have been able to determine this fact by repeated tests on most of the

subjects (chart, *B*, *C* and *D*) However, to obtain fairly constant reactions, it is necessary to note that excitement alone will raise the blood pressure markedly It is, therefore, clear that the first test may give a markedly greater elevation of blood pressure than subsequent tests, because part of the rise is due to excitement and part of it to the test itself On the other hand, the reaction may become greater on subsequent visits or tests if a lower and more nearly correct basal level of blood pressure is obtained A repetition of the test within a few minutes will accustom the patient to the procedure and give results more comparable to those obtained on later visits On the whole, however, subjects who give marked reactions continue to give abnormal reactions despite repetition on the same or subsequent visits The effect of excitement is greater in the hypertensive than in the normal subject

The constancy of the rise in blood pressure following breath holding is dependent also on the basal level of blood pressure obtained just before the test The closer the basal blood pressure is approached, the greater will be the rise on breath holding Even when a true basal level seems to be obtained and excitement avoided, we find that there may be a marked difference in reaction at different visits in certain subjects This we have found to be true previously also with the cold test However, despite all these variations, the general pattern of blood pressure reaction remains the same

We have studied also the effect of increasing the breath-holding time beyond twenty seconds It is found that many subjects, both normal and hypertensive, if able to hold breath much beyond twenty seconds experience an increasing rise of pressure In the hypertensive subject such increases may go to tremendous heights In the normal hyporeactor group such rises may be marked but rarely are On the other hand, there are many normal hyporeactors in whom prolonging the breath-holding time to from forty to ninety seconds results in but slightly greater rise than the twenty second test Here again the tendency is for the hypertensive subject to have the hyperreaction with prolonged breath holding, as compared with the normal, hyporeacting subject

#### COMPARISON OF THE BREATH-HOLDING AND THE COLD PRESSOR TEST

Throughout our study of the breath-holding test we have repeated on each subject the cold pressor test We have carried out in this way on the 150 subjects a total of 313 cold tests<sup>2</sup> and 650 breath-holding tests In all cases we have carried out the breath-holding test first, so that we would not be in any way influenced to maintain a slightly longer breath-holding period in an attempt to obtain a result equal to that of the

cold test On the whole, there has been a striking similarity of reaction with the two tests By similarity we mean that when the breath-holding test gave a hyperreaction, the cold test usually did the same In general, however, the breath-holding test gives a greater reaction, although of a similar degree There have been a number of cases, however, in which the cold pressor test gave little or no reaction and the breath-holding test gave a hyperreaction

To compare properly the reactions to these tests in a given subject it is necessary to obtain a similar basal level before each test This, however, is not easy, in hypertensive subjects especially The blood pressure of such subjects varies so markedly during the course of an hour that it is only in a small number that one can obtain a similar basal level Of 44 hypertensive subjects in whom we were able to obtain similar basal levels with each of these tests at the same visit, we found a marked similarity of reaction in 28 Fifteen others had a greater rise with the breath-holding test Three patients in whom there was practically no rise with the cold test had a marked response with the breath-holding test Of the 44 patients, 37 had hyperreactions to both the breath-holding and the cold pressor test, while 43 had hyperreactions to the breath-holding test One patient, with "fixed" hypertension and chronic nephritis, whose blood pressure did not drop during the resting period before the test, had a hyporeaction to both the breath-holding and the cold pressor test On the whole, however, even though the basal level of blood pressure is not precisely the same before each of these tests, we have found in the other hypertensive patients that hyperreactions to both tests occur in most cases

#### MECHANISM OF THE TEST

Although breath holding in various forms has been used since the classic experiment of Valsalva, the use of breath holding by the method here described for the determination of its effect on the vasomotor system appears to be new The test was devised purely on the assumption that since hypertensive subjects seem to be sensitive to all stimuli and among the known stimuli to the vasomotor center is lack of oxygen, or increase of carbon dioxide, hypertension might be diagnosed by application of this stimulus It appeared to us that simple holding of the breath in normal expiration would increase the carbon dioxide content of the alveolar air and that the increase would be quickly reflected in the blood and the vasomotor center, with a resultant stimulus to blood pressure We were aware of Raab's<sup>3</sup> experiments, in which he showed

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3 Raab, W Die Beziehungen zwischen CO<sub>2</sub>-Spannung und Blutdruck bei Normalen und Hypertonikern Beitrag zur Pathogenese der nicht „nephritischen“ Hypertonien, *Ztschr f d ges exper Med* 68 337, 1929

that when carbon dioxide is inhaled there is a greater rise of blood pressure in hypertensive than in normal subjects. Therefore, we devised what seemed to us the simplest method of securing carbon dioxide stimulation, the method of breath holding. We have not, as yet, determined whether this is the mechanism of the rise in blood pressure in this test. It is clear that changes in intrathoracic pressure must be considered. However, we have always tried to be certain that the breath was held just after slight and quiet expiration. This should not be associated with abnormal intrathoracic pressure, which would be present if there was a forced inspiration or expiration. However, it must be recognized that during the last few seconds of the twenty second period most subjects become uncomfortable, and that mild squirming may be associated with changes in intrathoracic pressure. This we will attempt to determine. The mechanism appears to be different from that of the cold pressor test, for when we have carried out the two tests at the same time on the same subject we have obtained a summation of effects.

#### COMMENT

The foregoing statements indicate that the twenty second breath-holding test furnishes an excellent standard stimulus of blood pressure and appears to cause a rise of blood pressure from two to four times greater in the hypertensive subject than in the normal subject of similar age. It causes as great a rise in blood pressure as does the cold pressor test and in many cases a greater reaction. In this respect it appears to be more effective. From the aspect of convenience, it is clearly simpler to carry out and requires no apparatus. It is, therefore, more practical for bedside or office use.

The question of discomfort arises with any stimulation test. We have found that many people consider the cold test extremely painful and almost unbearable. Others have reported acute reactions and much discomfort. We have questioned patients frequently as to the relative discomfort experienced with the cold test and with the breath-holding test, there appears to be an equal division of opinion. It is clear that holding one's breath becomes uncomfortable from the twelfth second onward and that twenty seconds is the average maximum period. It is likewise clear that the test cannot be conveniently carried out on persons who have shortness of breath from any source. The test, moreover, requires some cooperation of the subject, who must obviously not breathe in or out even slightly.

The significance of the breath-holding test is the same as that of the cold test, whatever the value of either may be. From direct studies of families, family histories and the follow-up reports of some hyper-



reactors over a period of time, it has been shown that hyperreaction to the cold test is of some significance <sup>4</sup> This holds true also for the breath-holding test The present report is purely in the nature of a preliminary discussion

#### CONCLUSION

Holding the breath in quiet expiration, with the nose and mouth closed, for twenty seconds is a simple standard stimulus of blood pressure Hyperreactors and hyporeactors can be determined by this method The test is simple and furnishes a somewhat greater stimulus than the cold pressor test

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<sup>4</sup> Hines, E A, Jr, and Brown, G E A Standard Test for Measuring the Variability of Blood Pressure, *Ann Int Med* **7** 209 (Aug) 1933 Hines, E A, Jr The Hereditary Factor in Essential Hypertension, *ibid* **11** 593 (Oct) 1937

# RENAL CHANGES FOLLOWING ADMINISTRATION OF HYPERTONIC SOLUTIONS

(50 PER CENT SUCROSE, 50 PER CENT D SORBITOL,\* 50 PER CENT DEXTROSE  
AND 10 PER CENT SODIUM CHLORIDE)

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AND

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CHICAGO

Because of the widespread use of hypertonic solutions for intravenous administration in modern clinical practice we became interested in the question whether renal damage resulted from the employment of such solutions and, if so, what the nature and extent of this damage might be. In recent years the intravenous administration of hypertonic solutions of dextrose has become increasingly popular. Lately 50 per cent sucrose has gained wide vogue in the treatment of cerebral edema, glaucoma and retention of fluid resulting from a variety of causes.<sup>1</sup> This material has been rapidly replacing the older dextrose solution for this type of therapy.

Helmholz<sup>2</sup> reported on a series of experiments on rabbits given single and multiple injections of 50 per cent solution of sucrose at various intervals and pathologic studies of the kidneys made at intervals of one to seven days after the final injection of the material. Included in his report was 1 case studied clinically in which it is believed that repeated injections of sucrose (for the relief of high intracranial tension due to meningitis) caused a significant depression of renal function. Our consideration of this work was largely motivated by the following wishes: (1) to use more sturdy experimental animals (dogs), since rabbits are notoriously susceptible to renal injury from even slight insults, (2) to control each experiment with biopsy of the kidneys preliminary to the injections, (3) to use doses in experiments with both animals and human subjects which were comparable with the clinical dose now con-

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\* Abbott Laboratories supplied this material. The compound d-sorbitol is an alcohol obtained by the reduction of dextrose, is optically dextrorotary and has the following formula:  $\text{CH}_2\text{OH}-(\text{CHOH})_4-\text{CH}_2\text{OH}$

1 Jackson, H. Ann Surg **106** 116 (Aug) 1937

2 Helmholz, H. J Pediat **3** 144 (July) 1933

sidered effective and widely employed, rather than the relatively enormous dose which Helmholtz gave his rabbits, (4) to test the effects on human subjects both with and without evidence of impairment of renal function

At the close of the experiments with sucrose our attention was drawn to a new substance, d-sorbitol. It was then decided to make a comparable series of animal experiments with this material in 50 per cent solution. Further to enlarge the scope of this comparison to include the third principal form of sugar now in use for the purposes originally stated, a series of experiments were similarly performed with 50 per cent solution of dextrose. The only other hypertonic solution which is widely injected intravenously is 10 per cent solution of sodium chloride, used in the treatment of peripheral vascular disturbances.<sup>3</sup> Accordingly, the kidneys of the dogs in which this material had been injected were investigated in the same manner as in the other series.

#### HUMAN EXPERIMENTS

A series of 15 persons with no known renal damage were given 200 cc of 50 per cent sucrose intravenously in a single dose. The urine and urea clearance of each of these persons were studied before the administration of the sucrose and twenty-four hours after its administration (several hours after the diuretic effect had subsided). In no case was there evidence of marked impairment of renal function. An occasional specimen of urine after the injection showed a 1 plus reaction for albumin or hyaline casts. The urea clearance remained essentially stationary, and in some cases it was increased by 3 to 5 per cent.

After this 5 patients with known renal damage were similarly studied. In these, too, the urine and urea clearance showed no significant changes as a result of the injection of 200 cc of sucrose intravenously.

#### ANIMAL EXPERIMENTS

In spite of the essentially negative clinical results of single doses, we were stimulated by Helmholtz' report to study the anatomic effects on normal animals. For this purpose 15 healthy dogs were used. Renal biopsy was performed on each, and after a sufficient period of recovery 100 cc of 50 per cent solution of sucrose was administered intravenously daily for ten to twelve days. Three days after the last injection the dogs were killed and microscopic sections of the intact kidney made. One animal (dog 1) was given injections for fourteen days and was killed seven days after the last injection. Of the 5 dogs, this one showed the most marked changes (table, dogs 1, 2, 4, 3 and 15). Four of these

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3 Siebert, S. Surg., Gynec. & Obst. 61:214 (Aug.) 1935

*Results of Administration of 50 per Cent Solution of Sucrose to Dogs in Which  
Previous Renal Biopsy Had Shown No Abnormality*

Dog	Daily Dose, Cc	Duration of Medl cation, Days	Interval from Start of Medication to Death	Albumin	Erythro cytes in Urine	Casts	Microscopic Diagnosis
1	100	14	21 days	0	0	+ to +++++	Two thirds of glomeruli showed hemorrhagic necrosis, some tubular degeneration and necrosis
2	100	12	15 days	+ to ++	1 to 5	0 to +	One sixth of glomeruli contracted, with associated tubules showing retrogressive changes
4	100	12	15 days	+ to ++	2 to 30	0	Hyperemia, hemorrhages into tuft, early necrosis of tubules having swollen and granular cytoplasm
3	100	10	12 days	+ to ++	5 to 15	0	Few glomeruli showed retrogressive changes, some hemorrhages into glomerular tufts and changes, early degeneration of convoluted tubules
15	100	10	12 days	+ to ++	1 to 3	+ to ++	Tubules essentially normal, no marked changes seen in glomeruli
14	100	8	10 days	++ to +++	3 to 5	Occasional hyaline	Tubules essentially normal, no marked changes seen in glomeruli
5	100	6	8 days	0	0	0	Occasional hemorrhage into glomerular tuft, necrosis and swelling of some of the collecting loops with nuclear degeneration
8	50	12	16 days	0 to +	5 to 7	0	Many glomeruli showed changes varying from hemorrhages into tuft to coagulative necrosis, with pyknosis of cells of glomerulus, tubules in various stages of degeneration
7	50	10	16 days	0	15 to 20	0	Glomeruli showed degenerative changes in capillary walls and capsule, cells of convoluted tubules were swollen with granular cytoplasm
6	100	1	24 hours	0	0	0	Moderate hyperemia of glomerular tuft, proximal and distal convoluted tubules showed intense swelling nearly obstructing tubules, glomeruli were swollen and hemorrhagic
9	100	1	72 hours	0	0	0	Glomerular and interstitial capillary congestion, tubular cytolysis, granular degeneration, indistinct cell outlines and sloughing of lining epithelium, tubular nuclei swollen, pale and vacuolated
10	100	1	120 hours	0	0	0	Changes in all of cortical area but in patches at varying intensity, all changes moderate (changes similar to those of dog 9, but not as intense)
11	100	1	168 hours	0	0	0	No significant abnormality

5 dogs showed changes in the kidney ranging from scattered areas of hyperemia and slight tubular changes to actual hemorrhagic necrosis of the glomeruli and marked tubular degeneration (fig 1) Dog 1 showed only casts in the urine Dog 15 showed no significant anatomic changes All the dogs showed some urinary changes, mainly loss of albumin and presence of some red blood cells



Fig 1 (dog 1) —Photomicrograph of section of kidney ( $\times 135$ ) removed seven days after the last injection of sucrose, which was given daily for fourteen days Hemorrhagic necrosis of the glomeruli and marked tubular degeneration can be seen

After this, 2 more dogs (7 and 8) were similarly subjected to renal biopsy and after recovery were given doses of 50 cc of 50 per cent sucrose for ten and twelve days, respectively They were killed six and

four days, respectively, after the last injection (sixteen days after the first injection in each case) The latter (dog 8) showed many glomerular changes, varying from hemorrhages into the tuft to coagulative necrosis with pyknosis and fragmentation of the endothelial cells of the glomerulus The former (dog 7) suffered degenerative changes in the capillary wall and glomerular capsule, and the tubular cytoplasm was swollen and

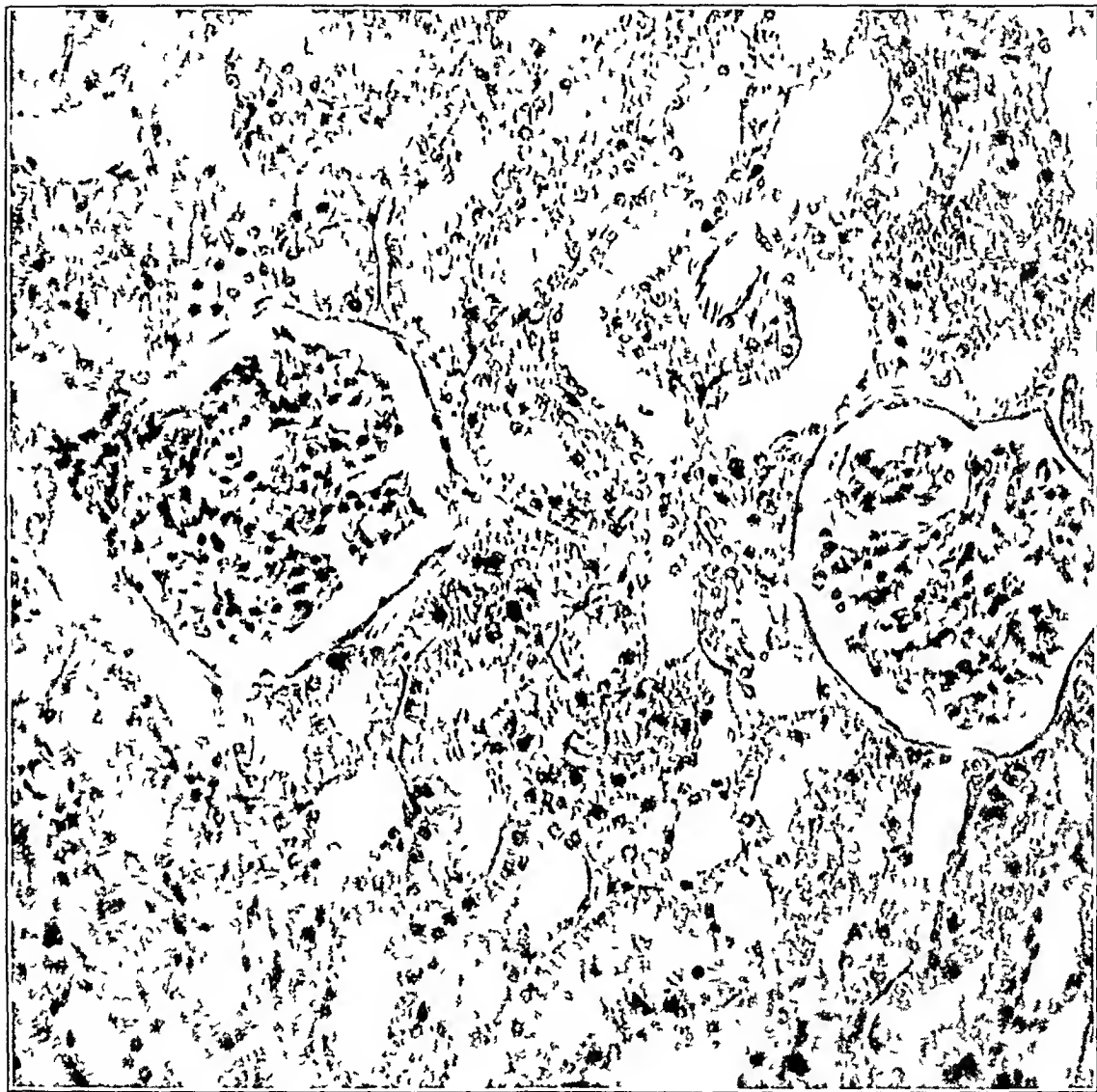


Fig 2 (dog 6) —Microscopic section of kidney ( $\times 270$ ) before intravenous injection of 100 cc of 50 per cent solution of sucrose

granular The urine of this animal showed 15 to 20 red blood cells per high power field in the daily sediment

Dogs 14 and 5 were then subjected to daily doses of 100 cc for eight and six days, respectively, and killed two days after the last injection Comparison of the microscopic sections of the kidneys taken before injection and after death showed no marked changes for dog 14, although

the daily urinary sediment had revealed a 2 to 4 plus reaction for albumin, red blood cells and casts, dog 5 showed moderate hyperemia and signs of early degeneration, with hemorrhages and early necrosis of the tufts in the glomeruli. Throughout the cortex, the proximal and distal convoluted tubules and loops of Henle revealed cells with swollen and granular cytoplasm which took a faint stain with eosin

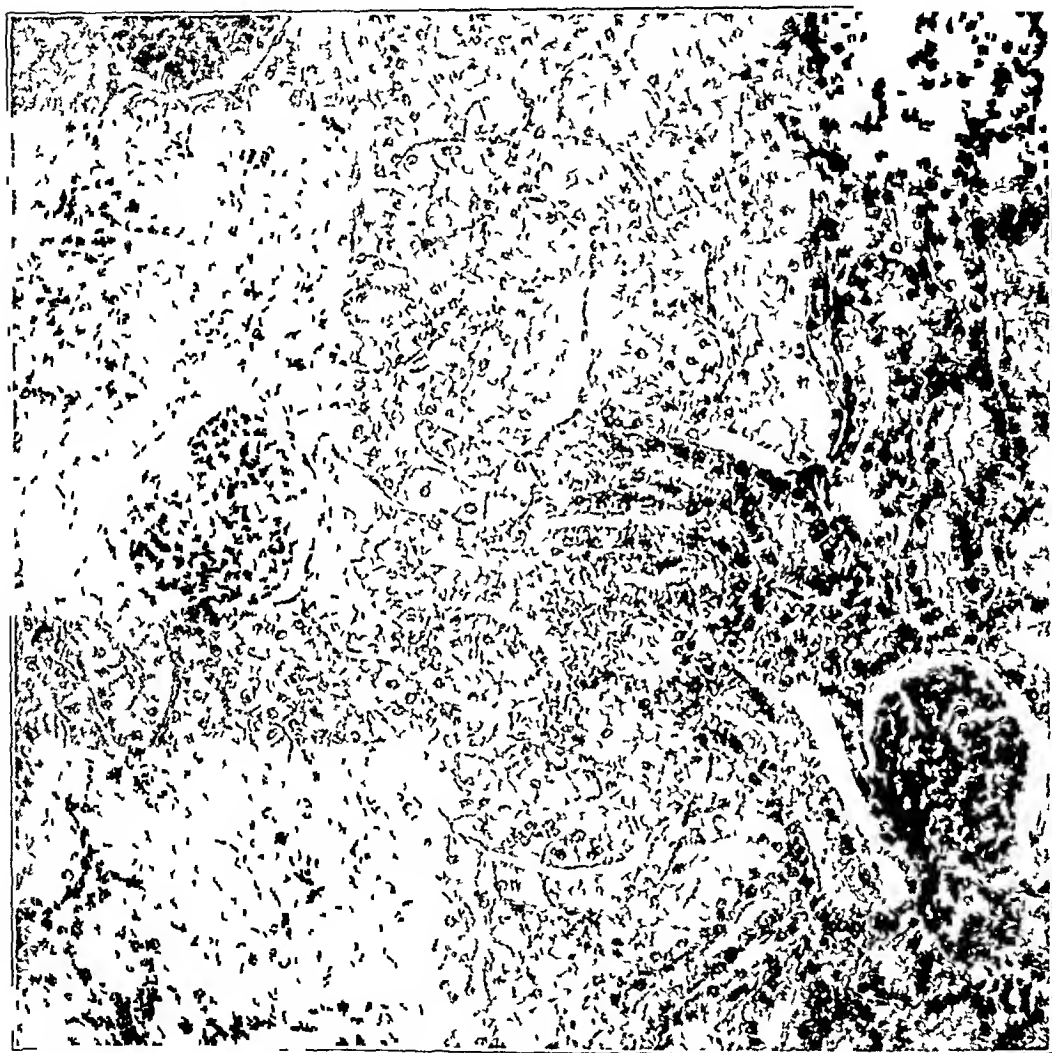


Fig 3 (dog 6) —Microscopic section of kidney ( $\times 210$ ) twenty-four hours after intravenous injection of 100 cc of 50 per cent solution of sucrose. The changes observed are those of marked hyperemia of the glomeruli and the tubules, as well as intense edema of the tubules draining the affected glomeruli, to the point of obliteration of the lumens in many cases. (Compare with figure 2)

The tubules draining the damaged glomeruli were in various stages of degeneration.

Finally, it was decided to study the renal changes which might result from a single injection of the substance. For this purpose 4 dogs

(6, 9, 10 and 11) were first subjected to renal biopsy and after recovery were given a single dose of 100 cc of 50 per cent sucrose. They were then killed after twenty-four, seventy-two, one hundred and twenty and one hundred and sixty-eight hours, respectively. Microscopic study of the kidneys at that time showed a rather clear course of events. After twenty-four hours the changes were those of hyperemia and marked

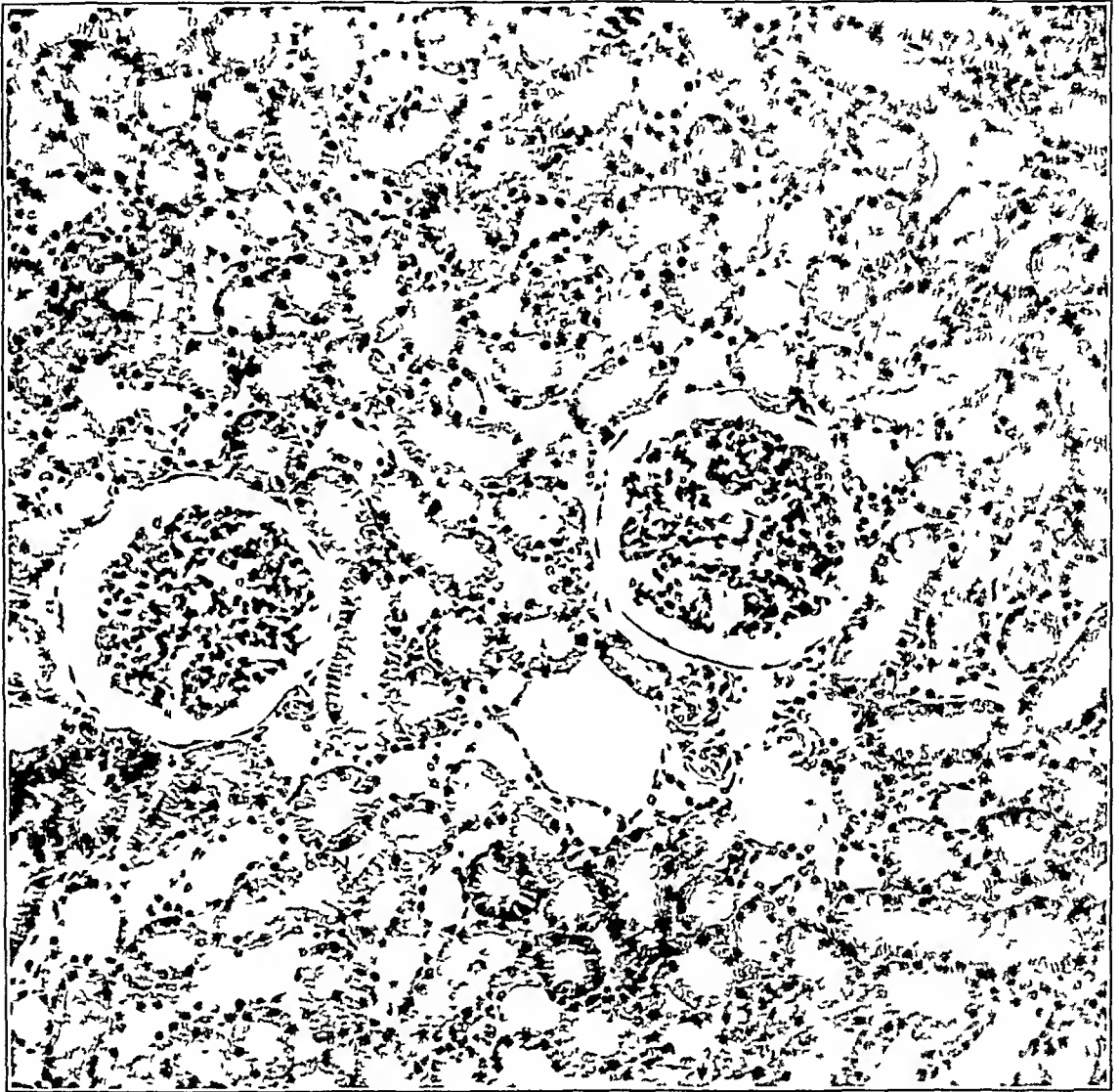


Fig 4 (dog 9) —Microscopic section of kidney ( $\times 210$ ) before injection of 100 cc of 50 per cent solution of sucrose

edema of the tubules, almost to the point of obliteration of the lumens. After seventy-two hours the changes had reached the peak, as evidenced by fairly marked glomerular and interstitial hyperemia, with sloughing of the lining epithelium of the tubules, the cells of which contained pale swollen nuclei. The changes noted after one hundred and twenty hours were definitely less, and after one hundred and sixty-eight hours restitution had taken place. These findings are in essential agreement with



those of Helmholtz Figures 2 and 3 (dog 6), 4 and 5 (dog 9) and 6 and 7 (dog 10) show the microscopic changes observed

#### ANIMAL EXPERIMENTS WITH D-SORBITOL

In the series of experiments with d-sorbitol, dogs (216 to 220) were subjected to preliminary biopsy of the kidney, and 100 cc of 50 per cent

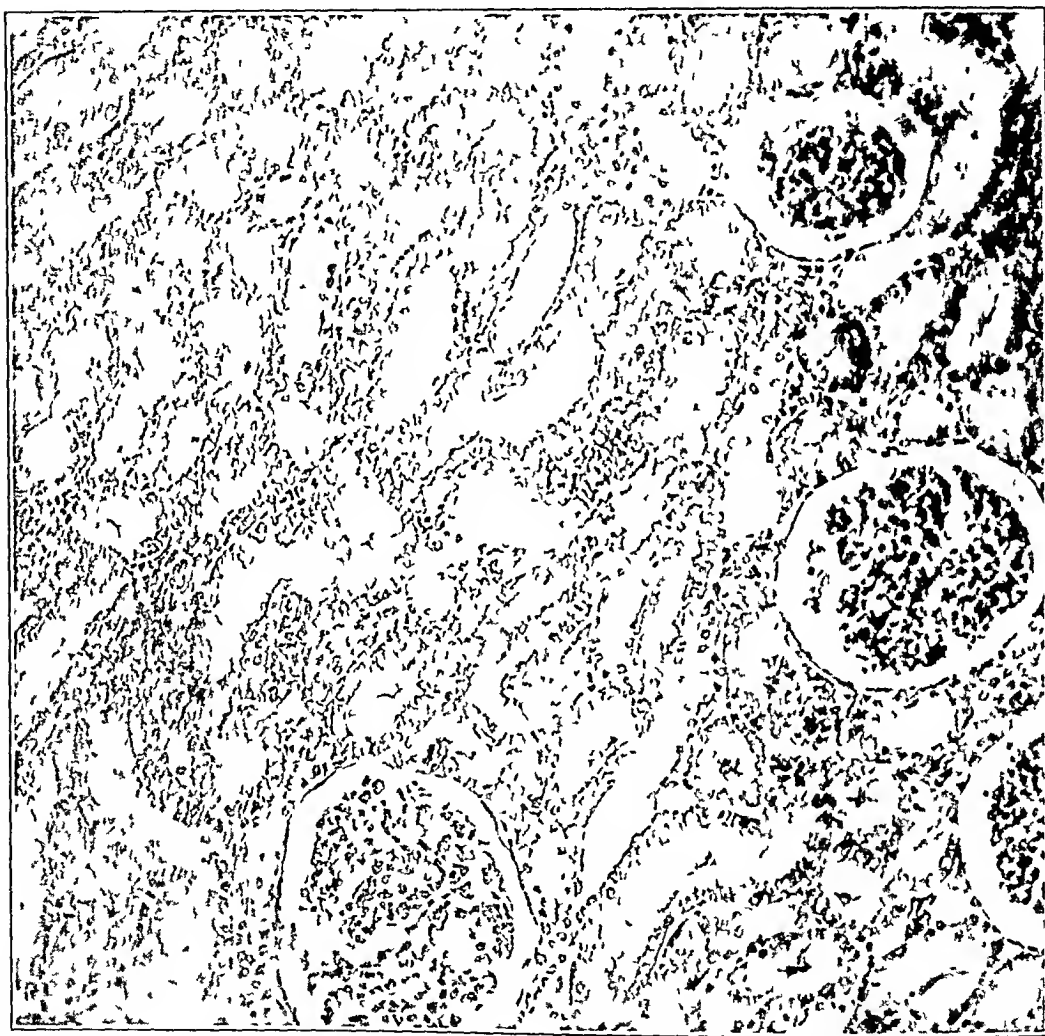


Fig 5 (dog 9) —Microscopic section of kidney ( $\times 210$ ) seventy-two hours after injection of 100 cc of 50 per cent solution of sucrose, showing moderate capillary congestion. The tubular epithelium shows cytolysis and sloughing of tubular epithelium, in some cases leaving only the basement membranes as an outline of the tubule (Compare with figure 4)

solution of d-sorbitol was injected. The dogs were killed twenty-four, forty-eight, sixty-nine, one hundred and twenty and ninety-six hours after injection, respectively. Comparison of sections of kidney removed

from these animals at the time of death with the biopsy specimens revealed no alterations. Two more dogs (221 and 222) were given 50 per cent solution of d-sorbitol intravenously in doses of 100 cc daily for ten and nine consecutive days, respectively. The latter dog died fifteen hours after the last injection, and at autopsy an abscess was seen at the site of the original incision for biopsy. The former dog (221) was

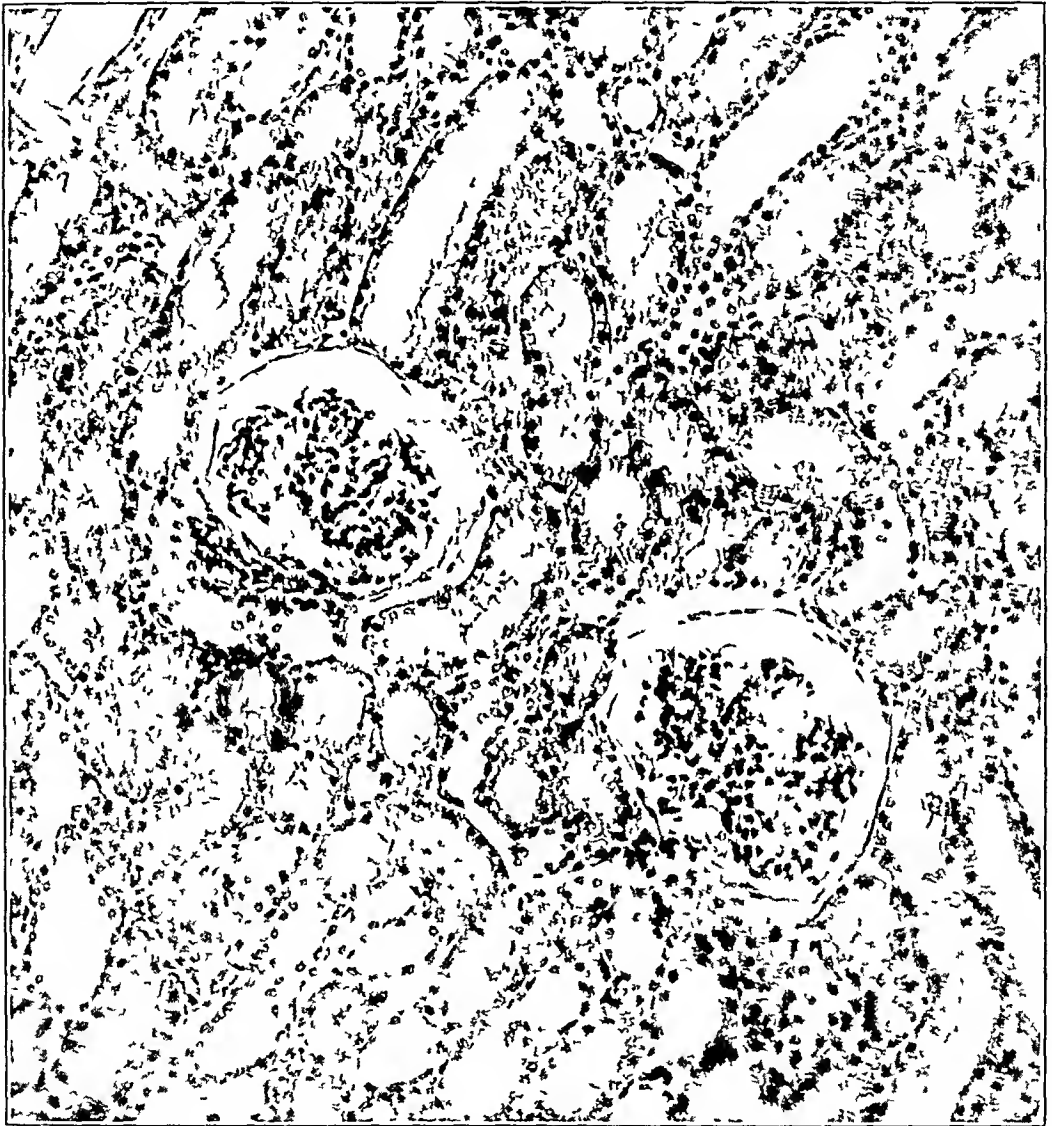


Fig 6 (dog 10) —Microscopic section of kidney ( $\times 210$ ) before administration of 100 cc of 50 per cent solution of sucrose

killed twenty-four hours after the last injection. Neither of the dogs showed significant alterations in the kidneys at the time of death according to microscopic comparison of postmortem sections with biopsy specimens taken preliminary to the experimental period.

#### ANIMAL EXPERIMENTS WITH 50 PER CENT SOLUTION OF DEXTROSE

Since the action of sucrose on the dog's kidney was already known to us, it was felt that if the outlines of the experimental procedure used

in the study of the effects of that substance were followed with dextrose and with sodium chloride, ample data for comparison would be available without undue sacrifice of time and of animals. Accordingly, in each of the following series only 3 dogs were used. One dog of each series was given injections daily for ten days and killed forty-eight hours after the last injection. Two other dogs in each series were given single injec-

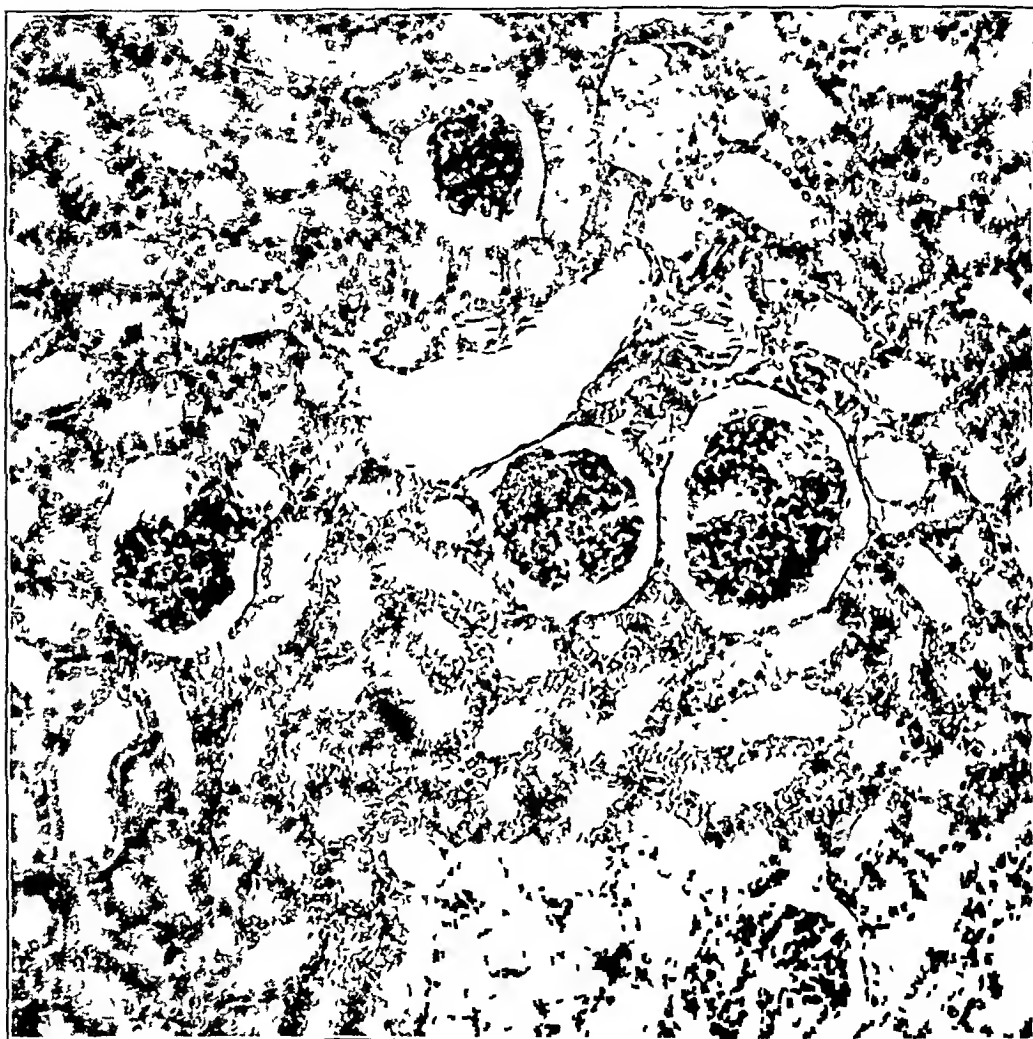


Fig 7 (dog 10) —Microscopic section of kidney ( $\times 210$ ) one hundred and twenty hours after administration of 100 cc of 50 per cent solution of sucrose, showing changes in tubules similar to those in figure 5. However, cells of the tubules show evidence of restitution. The glomeruli are definitely contracted, with evidences of early degeneration of glomerular epithelium. (Compare with figure 6.)

tions and killed twenty-four and seventy-two hours later. From our experience with the injection of sucrose we were satisfied that we could detect renal lesions if they occurred, whereas if they did not occur under

these experimental conditions we could feel equally safe in stating that the compounds we were injecting were innocuous. In addition, abundant pathologic material from patients to whom 50 per cent solution of dextrose or 10 per cent solution of sodium chloride had been administered before death attested to the harmless nature of these substances, at least in relation to the kidneys.

Dog 223 was given ten daily injections of 100 cc of 50 per cent solution of dextrose intravenously and killed forty-eight hours after the last injection. Dogs 225 and 227 were each given a single injection of 100 cc of 50 per cent solution of dextrose intravenously and killed twenty-four and seventy-two hours later, respectively. Comparison of the microscopic sections of the kidneys taken at the time of death with those obtained by biopsy before injection failed to reveal significant alterations, in contradistinction to the effects observed in the comparable series of experiments in which sucrose was used.

#### ANIMAL EXPERIMENTS WITH 10 PER CENT SOLUTION OF SODIUM CHLORIDE

In like manner dogs 224, 226 and 228 were given intravenous injections of 50 cc of 10 per cent solution of sodium chloride. Dog 224 received ten daily injections and was killed forty-eight hours after the last injection, while dogs 226 and 228 were given single injections and killed twenty-seven and seventy-two hours later, respectively. Here, too, no alterations of the kidneys were noted when sections were compared with biopsy specimens taken from these dogs before injection.

#### COMMENT

It is obvious from this work that the intravenous administration of 50 per cent solution of sucrose to dogs in doses comparable to those used clinically may be expected to produce renal lesions. These lesions reach the peak of severity three to five days after injection and, if permitted, will subside entirely by about the seventh day. Embarrassment of renal function, if present at all, is not measurable by present clinical methods in either dog or man. Prolonged daily administration tended to produce variable but marked renal lesions, with a delay in ability to make restitution. It is easily conceivable, therefore, that repeated administration of sucrose at intervals of several days might, by the summation of insults to the kidney and by the delay in restitution of the previously injured tissue, eventually cause considerable functional impairment of the kidneys. There was slight evidence in 1 case (dog 1) that permanent changes may ensue after prolonged administration. This animal's kidney showed evidences of hyalinization of occasional glomeruli. It is felt that in spite of the marked tubular changes seen regeneration of these structures was complete.

A marked inconsistency was noted between the urinary findings and the degree of renal involvement revealed histologically. No predictions concerning one could be made on the basis of the other. It can be assumed that if changes comparable to those noted in the dog are present in the normal human being impairment of renal function in the latter may occur. Unfortunately, the tests were not extended over the entire week following the injections, so that evidence of impairment of function during the time when the renal lesion could be expected to be maximal was not obtained. On the other hand, even human subjects with impaired renal function showed no further functional embarrassment as a result of the injection.

#### CONCLUSIONS

1 A single dose of 200 cc of 50 per cent solution of sucrose administered intravenously to normal human beings and to those with existing impairment of renal function produces no significant change in the results of renal function tests.

2 Anatomically, after a comparable clinical dose of sucrose injected into dogs, changes in the kidneys, by comparison of postmortem sections with the normal biopsy specimen taken in each case, were seen to be fairly marked.

3 The morphologic changes are transitory, reaching their height between the third and the fifth day after injection of sucrose, with a marked tendency to complete restitution. Only after prolonged repeated administration does there seem to be some evidence of permanent glomerular change. Prolonged administration tends in some cases to delay restitution.

4 Although the likelihood of impairment of renal function by the clinical application of 50 per cent solution of sucrose is slight, the fact that morphologic changes are produced should be borne in mind and its indiscriminate use avoided.

5 The results of our experiments with the intravenous administration of 50 per cent solution of d-sorbitol to dogs, controlled with renal biopsy before injection, indicate that no renal alterations occur even after prolonged (ten days) daily injections of these doses.

6 The essential procedures carried out in the foregoing experiments were repeated for two additional series of dogs, 50 per cent solution of dextrose being used in one and 10 per cent solution of sodium chloride in the other. No renal injury could be noted by comparison of the microscopic appearance of the kidneys after death with that of biopsy specimens from the same dog before injection.

# INFLUENCE OF THE LIVER ON SERUM PHOSPHATASE

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AND

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BROOKLYN

The variable values for serum phosphatase in cases of hepatic disease have never been satisfactorily explained. Experimental work by previous investigators has not led to results that would clarify the interpretation of the serum phosphatase level in clinical hepatic and biliary disorders. Both clinically and experimentally, serum phosphatase rises in cases of extrahepatic biliary obstruction. The variable results obtained clinically in cases of hepatic disease led us to investigate the influence of the liver on the serum phosphatase by attempting to correlate the underlying pathologic picture in the liver with the resultant value for serum phosphatase.

## PROCEDURES AND RESULTS

All the experimental procedures were carried out under anesthesia induced by intravenous administration of pentobarbital sodium and under aseptic technic.

In experiment 1, 3 dogs were used, 2 male and 1 female, each weighing approximately 30 pounds (13.6 Kg). They were observed for ten days to establish the normal values for total cholesterol, free cholesterol, phosphorus, urea nitrogen and phosphatase, the normal icterus index, the variations of the metabolites during different parts of the day and the effects of the diet. Then by a pararectal or subcostal incision the abdomen was opened, and a single hepatic duct in 2 of the dogs was doubly ligated. In the third dog, one of the major hepatic ducts and the cystic duct were doubly ligated. The dogs did well after the operation and made uneventful recoveries. Venous blood was drawn for the aforementioned determinations every forty-eight hours for eight days after the operation and afterward at greater intervals.

The results show that after obstruction in a part of the biliary system a significant rise in phosphatase, total cholesterol and percentage of free cholesterol occurred. The icterus index did not rise. All the values returned to normal after six to eight weeks.

Necropsy revealed that the hepatic lobes the ducts of which were ligated were markedly atrophied (fig 1). The hepatic architecture of these lobes was indistinct.

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From the Department of Laboratories, Divisions of Biochemistry and Pathology, Jewish Hospital of Brooklyn, Dr. Max Lederer, Director.

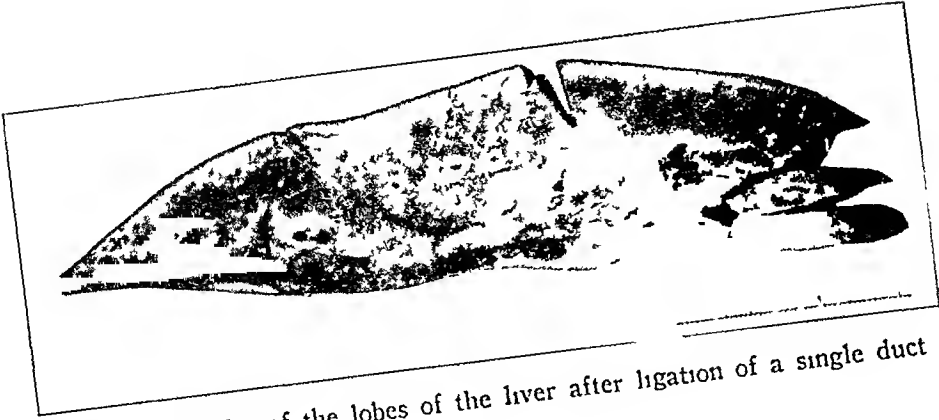


Fig 1—Atrophy of the lobes of the liver after ligation of a single duct

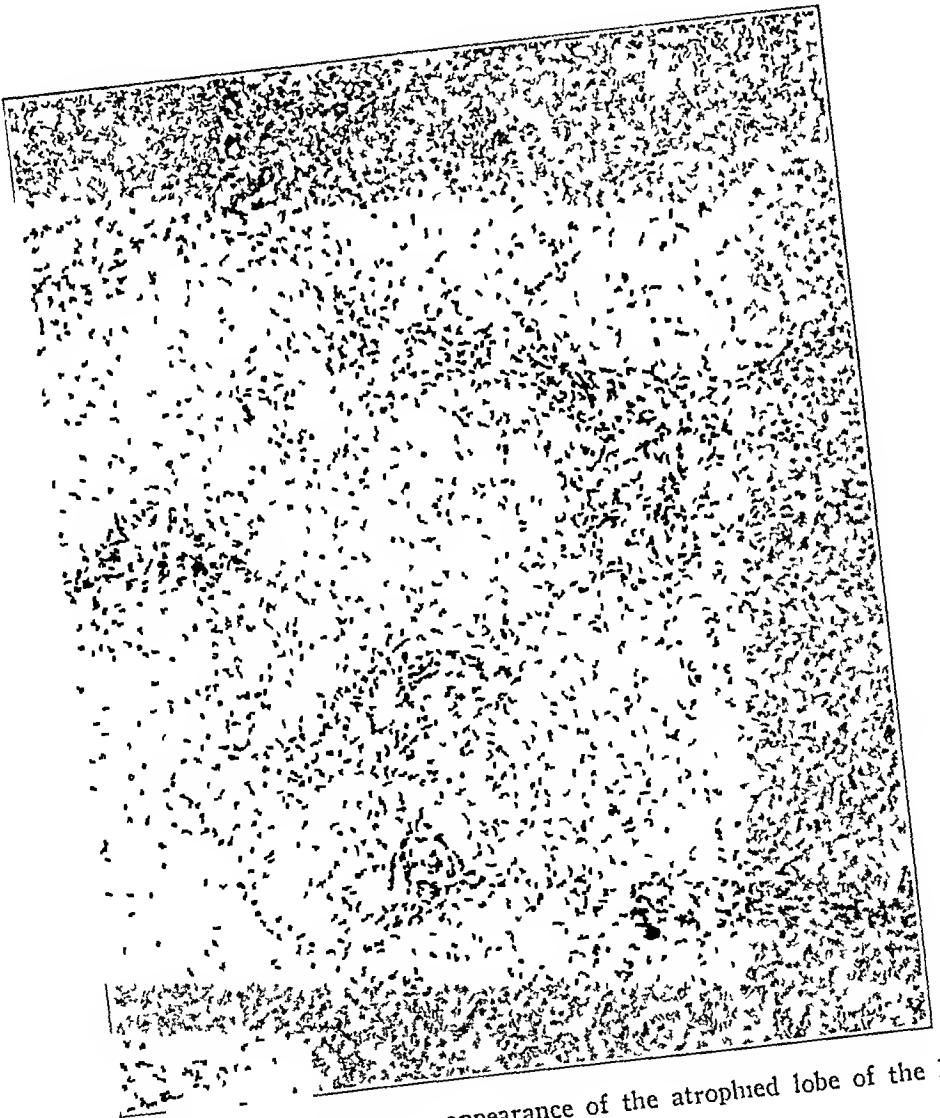


Fig 2 ( $\times 130$ )—Microscopic appearance of the atrophied lobe of the liver

The microscopic picture was that of marked atrophy of the lobules of the liver and congestion (figs 2 and 3) The lobules were small and surrounded by a relatively large amount of periportal connective tissue When cords of liver cells could be recognized, they were narrow and separated by broad sinuses filled with blood, so that the width of the cords compared to that of the sinuses was in reverse proportion The cytoplasm was either pale staining or vacuolated Only the nuclei

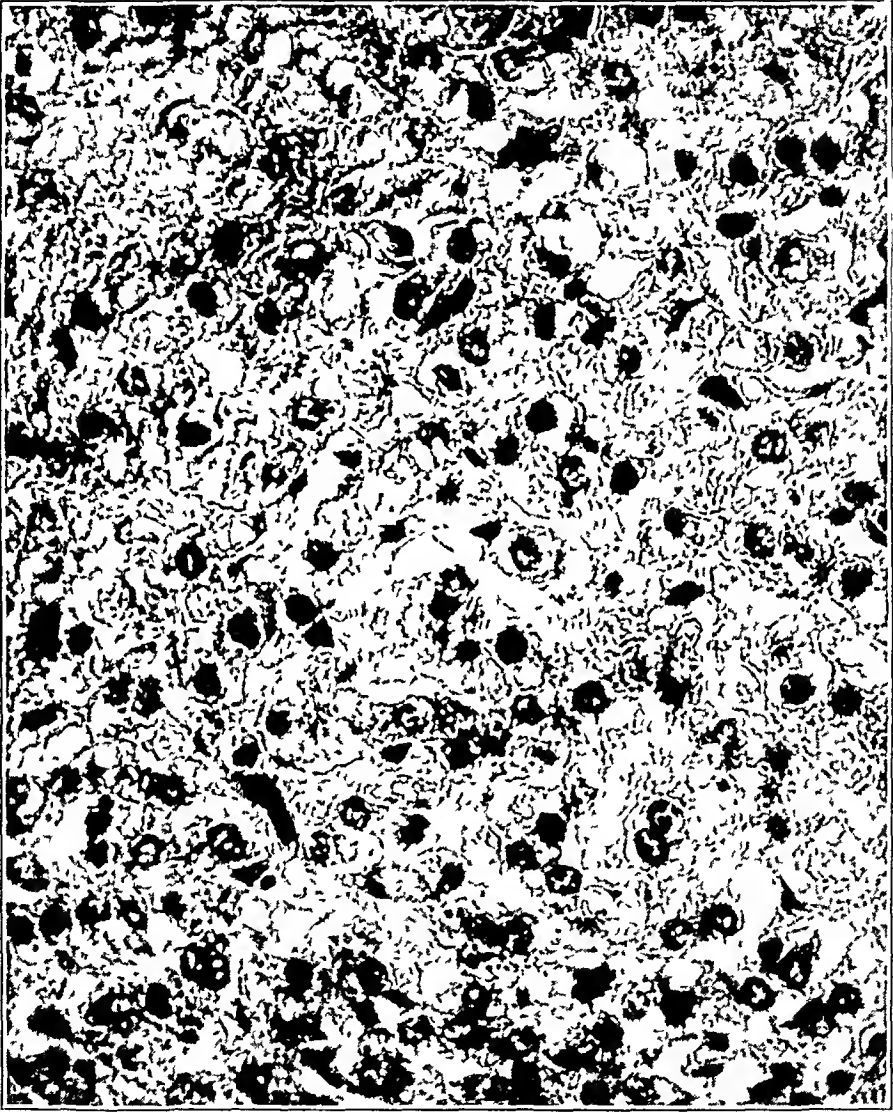


Fig 3 ( $\times 694$ ) —High power magnification of the section shown in figure 2

were rather well preserved The lumens of the bile ducts were not widened The latter showed no pathologic changes

In experiment 2, 3 dogs were used They were observed for several days, and the normal values for total cholesterol, free cholesterol, phosphorus, urea nitrogen and phosphatase and the normal icterus index were established The common bile and the cystic duct of dog 4 (weight 25 pounds [11.3 Kg]) were doubly ligated The dog recovered satisfactorily from the operation From two days after the operation on, 20 mg of arsenic trioxide was injected intravenously daily



A large necrotizing ulcer developed at the site of the operative incision. The dog died seven days after the operation.

The operative procedure was verified. Arsenic trioxide was found in the liver, kidney and skin.

After a complete biliary obstruction followed by intravenous injections of arsenic trioxide, the values for phosphatase rose to about ten times the normal value. There was a slight rise in the values for total cholesterol and in the percentage of free cholesterol.

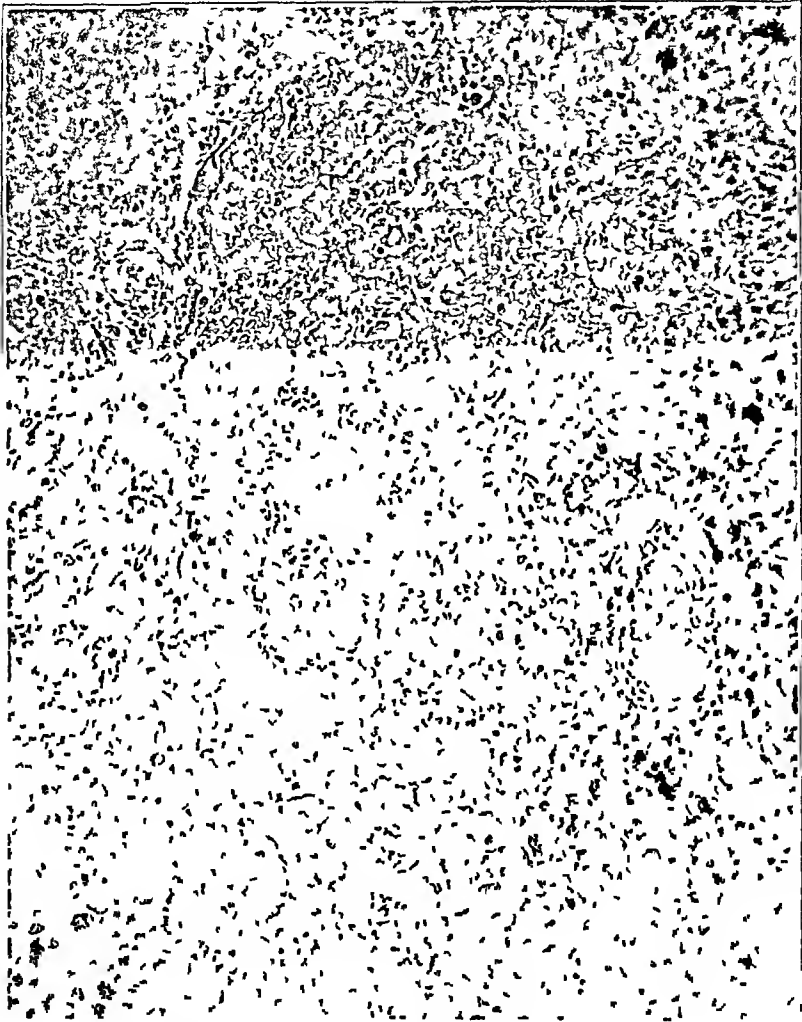


Fig 4 ( $\times 130$ )—Microscopic appearance of the liver after complete biliary obstruction and intravenous administration of arsenic trioxide.

In dog 5 (weight 30 pounds [13.6 Kg]), after the control values were determined, 20 mg of arsenic trioxide was injected intravenously daily for five days before the operation. The common bile and the cystic duct were doubly ligated—as in dog 4. Thirty-six hours after the ligation, the injections of arsenic trioxide were resumed. Forty-five milligrams of arsenic trioxide was injected in two days. The administration of arsenic was then discontinued. The dog recovered from the

operation After thirteen and one half days, when the dog seemed to be recovering, injection of 80 mg of arsenic trioxide in an attempt to produce severe damage was fatal in three hours

The operative procedure was verified Arsenic was found in the liver, skin and kidney

The results of the procedures were similar to the results obtained on dog 4, namely, after complete biliary obstruction and intravenous administration of arsenic

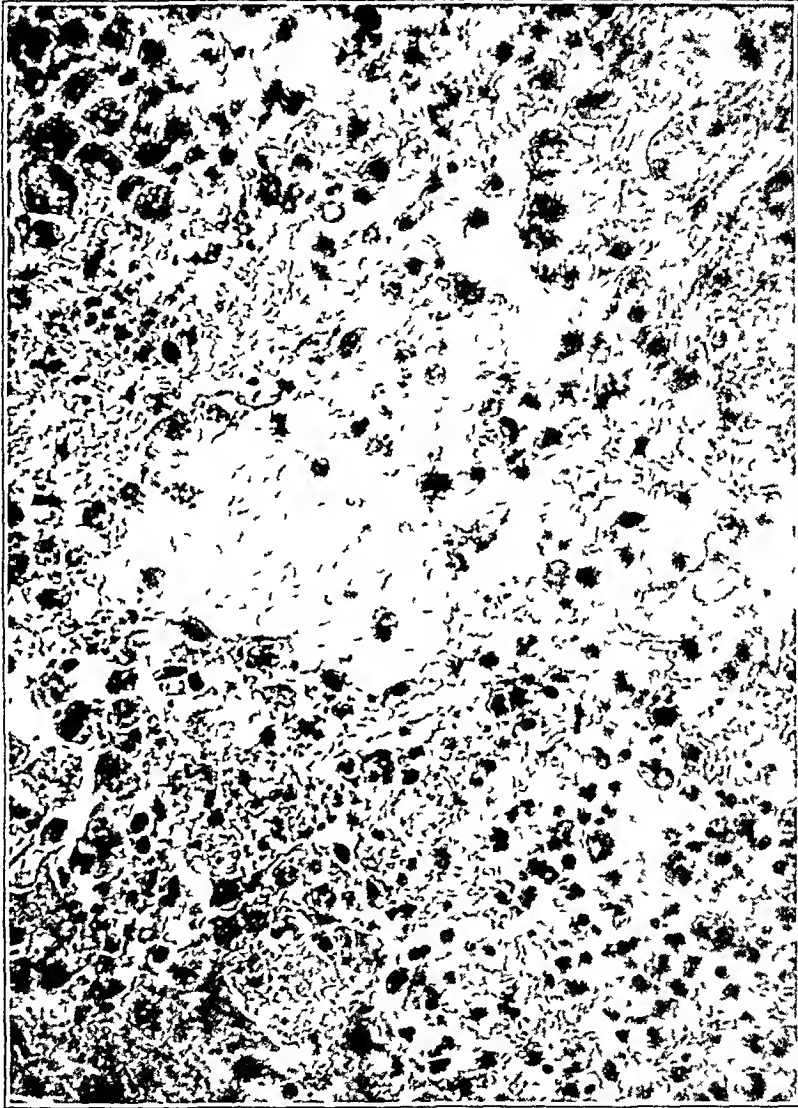


Fig 5 ( $\times 640$ ) —High power magnification of the section shown in figure 4

trioxide the serum phosphatase rose to about ten times the normal value A similar result was found in the cholesterol values

The microscopic appearance of the liver in this animal was that of central necrosis with hemorrhage The cords of liver cells in the central part of the lobules were destroyed and replaced by amorphous pink-staining material The cords toward the periphery of the liver lobules were separated by sinuses which were distended with blood Areas of extravasated blood also were present Many of the liver cells contained brown bile pigment The periportal connective tissue

TABLE 1—Results of Ligation of a Single Hepatic Duct

Time After Ligation, Days	Total Cholesterol	Free Cholesterol, %	Phosphorus	Phosphatase	Icterus Index
Dog 1					
Before ligation	160	23	3	35	25
1/2	179	22	3.1	166	20
2 1/2	227	23	3.4	516	39
4 1/2	220	31	3.1	560	25
7 1/2	288	23	4.2	458	25
13 1/2	396	25	4.9	404	33
18	312	21	5.0	294	20
23	248	20		130	20
30	276	21	4.2	68	22
39	227	21	2.6	38	2.0
Dog 2					
Before ligation	225	22	3.6	3.2	20
1	324		4.7	150	25
4	318	45	4.6	394	36
7	269	47	2.7	508	
10	327	31	4.6	470	
16	257	26	4.4	41.1	
40	254	20	5.5	180	25
55			3.7	3.7	20
Dog 3					
Before ligation	168	25	4.1	18	28
1	207	30	3.0	15.5	30
3	239		3.6	23.4	75
18	341	43	3.3	39.7	25
30	379	28	3.5	72.5	30
39	231	25		40.7	25
50	216	22	3.5	17.0	35
58	199	25	3.0	10.2	

TABLE 2 (dog 4)—Results of Ligation of the Common Bile and the Cystic Duct with Subsequent Administration of Arsenic

Time After Ligation, Days	Total Cholesterol	Free Cholesterol, %	Phosphorus	Phosphatase	Icterus Index
Before ligation	170	26	3.6	5.2	25
1	260	35	5.8	46.0	23.0
(Administration of Arsenic Started)					
3	278	22	4.1	43.4	23.0
4	275	32	5.3	47.2	33.0
5	280	26	6.3	46.2	30.0
6	230	31	8.0	44.5	31.0

TABLE 3 (dog 5)—Results of Ligation of the Common Bile and the Cystic Duct with Preparatory and Subsequent Administration of Arsenic

Time After Ligation, Days	Total Cholesterol	Free Cholesterol, %	Phos phorus	Phos phatase	Urea Nitrogen	Icterus Index
Before medication	213	38	5.0	2.7	22.2	
(Administration of Arsenic Started)						
Before ligation	187	26.2	4.4	1.1	13.5	
14 hr	250	43.2	5.0	36.0	11.0	58
1½	255	35.7	4.9	45.5	8.0	60
(Administration of Arsenic Resumed)						
3½	258	33.7	5.4	51.4	10.0	40
5½	306	36.0	3.6	48.9	7.5	55
8½	312	44.0	5.4	40.6	9.0	39
11½	266	37.0	4.2	49.0	6.5	32

was infiltrated with large mononuclear cells and a few polymorphonuclear leukocytes (figs 4 and 5)

In dog 6 of experiment 2 a similar obstruction was created. The dog made an uneventful recovery from the operation.

After complete biliary obstruction the serum phosphatase rose about forty-fold. The total cholesterol rose markedly and the percentage of free cholesterol moderately.

As a control, the abdomens of 2 dogs were opened, and the gallbladder and liver were manually and instrumentally handled. During the following fourteen days no changes in serum phosphatase were noted.

#### COMMENT

In the first experiment, the obstruction of only a small part of the biliary system produced a marked rise in serum phosphatase. Not

TABLE 4 (dog 6) —*Results of Ligation of the Cystic and the Common Bile Duct Without Medication*

Time After Ligation, Days	Total Cholesterol	Free Cholesterol, %	Phos phorus	Phos phatase	Urea Nitrogen	Icterus Index
Before ligation	215	27	3.9	3.9	22.0	
½	321		3.8	31.8	20.0	24.8
2½	308	33	4.5	57.5	20.0	39.0
5½	335	54		72.0	14.0	47.0
9	239	35	4.2	112.0	18.0	51.0
11	400		4.8	140.0	16.4	
16	478		5.6	200.0	15.0	

enough obstruction was produced to cause an accumulation of bile pigments (jaundice), since it has been proved experimentally that if one seventh of the biliary system in dogs remains open, jaundice does not occur<sup>1</sup>. Apparently, the metabolic functions of the liver were not seriously interfered with, except for the temporary rise in total cholesterol and in the proportion of free cholesterol. This phase of the work has been fully investigated clinically by Epstein and Greenspan<sup>2</sup> and experimentally by Hawkins and Wright<sup>3</sup>. According to the values recorded by the latter investigators, the results which we obtained were still within normal limits. However, the methods of determination which we used for cholesterol and ester concentrations differed from

1 Markowitz, J. Textbook of Experimental Surgery, Baltimore, William Wood & Company, 1937.

2 Epstein, E. Z., and Greenspan, E. B. Clinical Significance of the Cholesterol Partition of the Blood Plasma in Hepatic and Biliary Diseases, Arch Int Med 58:860 (Nov.) 1936.

3 Hawkins, W. B., and Wright, A. J. Exper Med 59:427, 1934.

those employed by the investigators mentioned. The values which we obtained were definite elevations as compared with those recorded for a series of 12 control dogs kept under observation for two weeks.

Figure 6 illustrates the typical rise in phosphatase when partial biliary obstruction is produced. After six to eight weeks the values return to normal limits. If one were to determine the value for serum phosphatase after fifty days of obstruction there would be no way of telling that an obstruction had ever existed. Therefore, serum phosphatase may be normal in the presence of a partial extrahepatic obstruction.

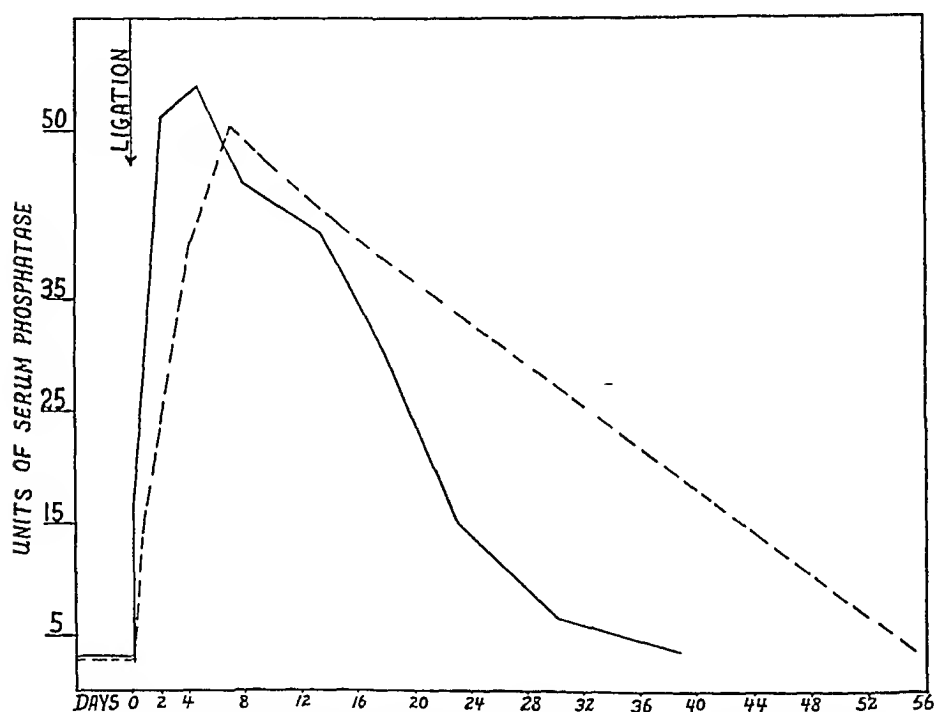


Fig 6—Changes in serum phosphatase after ligation of a single duct. The solid line represents observations on dog 1, the broken line, those on dog 2.

The cause of the steady decrease in the values for serum phosphatase in the presence of a permanent obstruction and of the occurrence of normal phosphatase when an extrahepatic obstruction is present may help to explain the variable results obtained in cases of hepatocellular disease. We believe that the results obtained were due to the lack of properly functioning liver cells secreting their products into the biliary channels which were obstructed. Therefore, in spite of the extrahepatic obstruction, still present after six to eight weeks, the phosphatase values were within normal limits. The gross and microscopic appearance of this portion of the liver indicated that the obstruction was still present.

but the corresponding portion of the liver had atrophied. In dog 3 in the first experiment, the same phenomenon occurred, but it took a longer time.

Experiment 2 confirmed the opinion that in addition to an extra-hepatic obstruction, there must be a good physiologic state of the liver cells for a rise in serum phosphatase to occur. When the liver cell was not damaged, an obstruction of the common bile duct caused a rise in serum phosphatase to more than twice the value that appeared with a

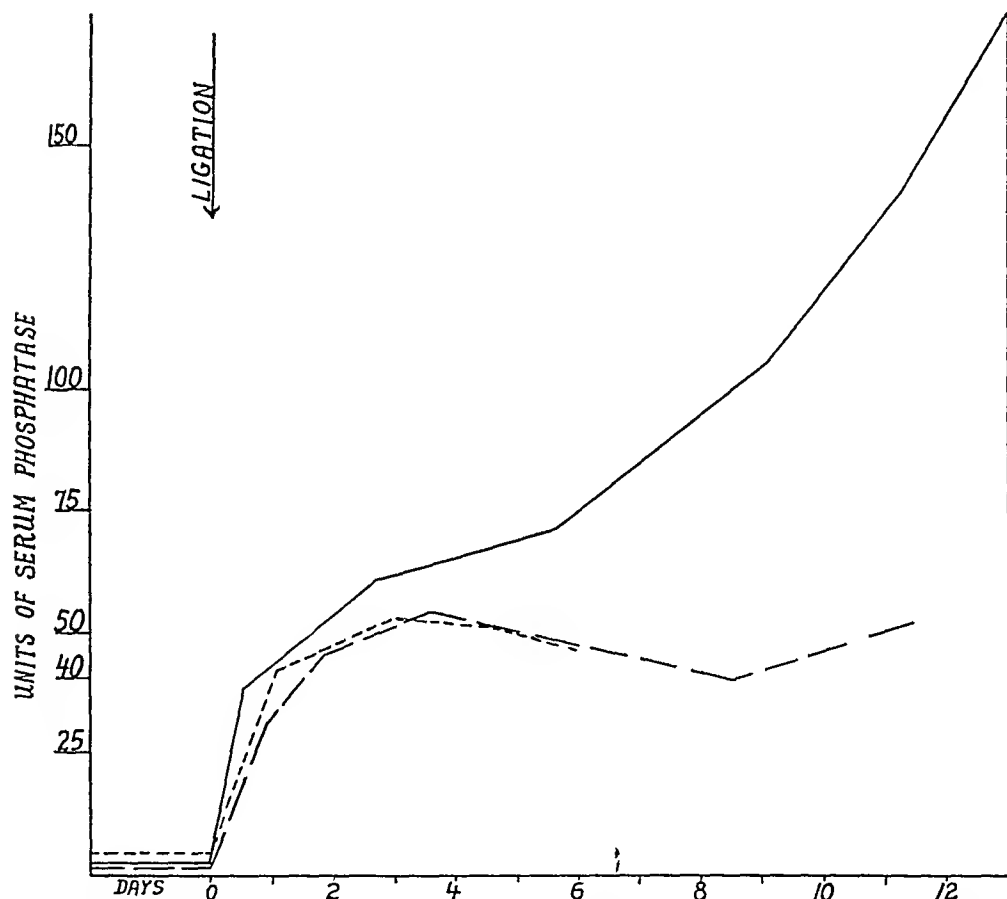


Fig 7—Comparison of results of complete biliary obstruction and intravenous administration of arsenic trioxide in dogs 4 and 5 and complete biliary obstruction in dog 6. The solid line represents observations on dog 6, the line of long dashes, those on dog 5, and the line of short dashes, those on dog 4.

similar obstruction when the liver cells were additionally damaged by arsenic trioxide. The cholesterol rose to higher levels in the case of obstruction without damage to the liver cells. Once again, our results were in accordance with Epstein and Greenspan's observations. Microscopic examination bore out the fact that in dogs 4 and 5, to which arsenic trioxide was given, the parenchyma of the liver was damaged.

Clinical and experimental evidence indicates that the liver cells play no part in the formation of bile pigment except that of secreting it into the bile ducts. This is not the case for phosphatase metabolism, and probably explains the difference in values in the hepatocellular type of jaundice.

Thannhauser and his co-workers<sup>4</sup> postulated that the increase in the amount of serum phosphatase in disease is not an actual increase in enzyme but merely an activation of enzyme normally present. The increased activity in jaundice is dependent on an activating substance (a cofactor, or coenzyme, which has not yet been determined) and a depressing substance (like bile salts). With obstruction, they concluded, there is a damming up of both, but since the cofactor is more powerful as an activating agent than bile acids are as depressors, the net result is an increase in activity of serum phosphatase.

It is difficult to place the knowledge of a cofactor and depressant substance in the picture shown by our experiments. Granted that there was a damming up of both substances in the case of extrahepatic obstruction, it seems likely that both substances would also accumulate in hepatocellular disease, in which some degree of obstruction usually exists. To theorize in this connection offers several interesting possibilities.

- 1 The coenzyme or activating principle may be destroyed when the liver cell is damaged.

- 2 In cases of damage to the liver cell there may be much greater production of the depressant substance, as for example the bile salts. This may account for the greater percentage of free cholesterol found in cases of this variety.

- 3 Perhaps a depressant substance which is so powerful in its action may pass from the small intestines, be brought to the liver and there be acted on in one of two ways, as the bile pigments are acted on by the liver. In cases of intrahepatic jaundice, this depressant substance may pass to the liver without being affected by the liver cells and therefore accumulate in the blood stream. In cases of obstructive jaundice, this substance is brought into the liver cell and is there acted on and consequently loses its depressant activity. This second process may resemble the change that the liver cell produces on bile pigments to make it diffusible and give the direct van den Beigh reaction.

The most likely explanation is that the production of an activating substance by the liver is diminished when the liver cell is damaged.

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<sup>4</sup> Thannhauser, S. J., Reichel, M., Grattan, J. F., and Maddock, S. J. *J Biol Chem* **121** 715, 1937.

## SUMMARY

1 Serum phosphatase values increase more than tenfold after ligation of a single hepatic duct. No other important changes in the blood result from this procedure.

2 After the rise that follows obstruction of a single hepatic duct, the values steadily decrease and in thirty to fifty-five days return to normal limits.

3 Obstruction of the common bile duct in a dog causes a rise in serum phosphatase more than twice that which follows a similar obstruction in other dogs whose livers have been damaged by intravenous administration of arsenic trioxide.

## CONCLUSION

The resultant values of serum phosphatase in hepatic and biliary disorders are dependent on two equally important factors: (a) the degree and extent of biliary obstruction and (b) the functional state of the liver cell.



# VITAMIN C AND THE AGING EYE

## AN EXPERIMENTAL CLINICAL STUDY

S MILES BOUTON JR, MD

DETROIT

In the course of routine refraction tests on a number of patients at the Hastings State Hospital during the late summer months of 1937, clouding of the optic media associated with more or less impaired vision was noted in an undetermined percentage of cases, apparently this was a precursor of senile cataract, a concomitant feature of early cataract or a morbid condition per se. The patients ranged in age from 41 to 73 years, represented both sexes and included workers and nonworkers. None was a newcomer to the institution. Only a small percentage of this group could be classed as actually senile. In view of references in the literature within the past few years to changes in the vitamin C content of the lens and of other structures of the eye in cataractous conditions (to be discussed later in this paper) and in view also of the combination of circumstances which conceivably might lead to vitamin C deficiency at this institution (geographic location, nature of diet and other factors), it was thought that an investigation into the status of the hospital population in this regard might prove enlightening.

Such an investigation seemed further indicated by the rather frequent occurrence of minor infections of the upper respiratory passages among the patients at this institution during the winter months, the occasionally extremely poor progress in the healing of decubitus ulcers and other lesions involving loss of skin, despite apparently insufficient clinical grounds for such delay, and the observation that some of these decubitus ulcers improved promptly and markedly after the administration of large quantities of tomato juice.

Attention is called to the work of Wolbach,<sup>1</sup> von Jeney and Toro<sup>2</sup> and Lanman and Ingalls<sup>3</sup> concerning the role of vitamin C in the forma-

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From the Hastings State Hospital, Ingleside, Neb., Juul C. Nielsen, M.D., Superintendent.

1 Wolbach, S. B. Controlled Formation of Collagen and Reticulum. A Study of the Source of Intercellular Substance in Recovery from Experimental Scorbutus, *Am J Path (supp)* **9** 689, 1933, Vitamin C and the Formation of Intercellular Material, *New England J Med* **215** 1158 (Dec 17) 1936, The Pathologic Changes Resulting from Vitamin Deficiency, *J A M A* **108** 7 (Jan 2) 1937.

*(Footnotes continued on next page)*

tion of intercellular material and thus in repair of wounds, and to the observations of Perla and Marmorston,<sup>4</sup> Juszat,<sup>5</sup> Hetler,<sup>6</sup> Cady,<sup>7</sup> McCullough<sup>8</sup> and Takahashi<sup>9</sup> on the role of vitamin C in the maintenance of resistance to infection and in the prevention of disturbances of the respiratory passages in cases of scurvy

In the optic media of the eye, which represent various types of tissue, any change in character, specifically any impairment of metabolism and nutrition, is readily manifested in decreased transparency and thus in measurable impairment of vision. It would seem logical, therefore, to search for a correlation between the degree of vitamin C saturation of the body and the presence of visual disturbances. The work here reported represents an attempt to determine the relation between the blood level of vitamin C, its excretion in the urine and the condition of the optic media, as well as the reaction of the latter to treatment with this substance.

No general review of the literature on vitamin C will be attempted in this report, but attention is called to the various comprehensive reviews at present available.<sup>10</sup>

The minimum daily intake of ascorbic acid required by a normal adult in order to maintain an adequate blood level is, according to

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2 von Jeney, A., and Toro, E. Die Wirkung der Ascorbinsäure auf die Faserbildung in Fibroblastkulturen, *Virchows Arch f path Anat* **298** 87, 1936, abstracted, *Arch Path* **24** 670 (Nov) 1937

3 Lanman, T. H., and Ingalls, T. H. Vitamin C Deficiency and Wound Healing, *Ann Surg* **105** 616 (April) 1937

4 Perla, D., and Marmorston, J. Role of Vitamin C in Resistance, *Arch Path* **23** 543 (April), 683 (May) 1937

5 Cevitamic Acid Stimulation of Specific Antibody Production, editorial, *J A M A* **109** 714 (Aug 28) 1937

6 Hetler, R. A. Nutrition and Infections of Respiratory Mucous Membranes, *Ann Otol, Rhin & Laryng* **46** 629 (Sept) 1937

7 Cady, F. C. Association of Scurvy with Oral Diseases, *Pub Health Rep* **52** 1526 (Oct 29) 1937

8 McCullough, N. B. Vitamin C and Resistance of the Guinea Pig to Infection with *Bacterium Necrophorum*, *Arch Path* **25** 139 (Jan) 1938

9 Takahashi, cited by Wachsmuth, W., and Heinrich, G. Hypovitaminose und Osteomyelitis, *Klin Wchnschr* **17** 269 (Feb 19) 1938, abstracted, *J A M A* **110** 1529 (April 30) 1938

10 (a) Wilder, R. M., and Wilbur, D. L. Diseases of Metabolism and Nutrition. Review of Certain Recent Contributions, *Arch Int Med* **61** 297 (Feb) 1938. (b) Booth, M., and Hansen, A. E. The Present Day Status of the Vitamins. A Review, *Journal-Lancet* **57** 530 (Dec) 1937. (c) Wright, I. S., and Lilienfeld, A. Pharmacologic and Therapeutic Properties of Crystalline Vitamin C (Cevitamic Acid), with Especial Reference to Its Effects on Capillary Fragility, *Arch Int Med* **57** 241 (Feb) 1936. (d) Perla and Marmorston<sup>4</sup>

Gothlin<sup>11</sup> and Abbasy and his co-workers,<sup>12</sup> about 25 mg. Schultzer's<sup>13</sup> recent work confirmed this. Apparently no symptoms are known to be associated with excessive intake. Determinations of the ascorbic acid level of the blood by various investigators have given roughly comparable results, so that it is possible at present to determine at least approximately what may be considered a normal level and what a minimum level, below which one may presume a deficient intake. According to Mirsky, Swadesh and Soskin,<sup>14</sup> the total ascorbic acid content of whole blood ranges between 1.11 and 2.88 mg. per hundred cubic centimeters. Farmer and Abt<sup>15</sup> found values of from 0.69 to 2.36 mg. per hundred cubic centimeters for reduced ascorbic acid content of blood plasma. Bellows,<sup>16</sup> in a comparison of the ascorbic acid levels in the blood plasma of normal and of cataractous persons, found average values of 1.02 and 0.605 mg. per hundred cubic centimeters, respectively. In another report by Farmer and Abt,<sup>17</sup> these authors stated that an ascorbic acid content of the blood plasma reduced to less than 0.50 mg. indicates "marked insufficiency of vitamin C intake," while Ingalls and Warren<sup>18</sup> stated that they considered levels below 0.30 mg. indicative of asymptomatic scurvy. Later references to the level of this substance in the blood<sup>19</sup> specified 0.70 mg. per hundred cubic centimeters as an

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11 Gothlin, G. F. Method of Establishing a Vitamin C Standard and the Requirements of Physically Healthy Individuals by Testing the Strength of the Cutaneous Capillaries, *Skandinav Arch f Physiol* **61** 225 (May) 1931, cited in Human Requirement for Vitamin C, editorial, *I. A. M. A* **110** 1928 (June 4) 1938.

12 Abbasy, M. A., Harris, L. J., Ray, S. N., and Marrack, J. R. Diagnosis of Vitamin C Subnutrition by Urine Analysis, *Lancet* **2** 1399 (Dec 21) 1935.

13 Schultzer, P. On Saturation of Scurvy Patient with Small Doses of Ascorbic Acid. Consideration of Daily Human Requirement, *Biochem J* **31** 1934 (Nov) 1937.

14 Mirsky, Swadesh and Soskin, cited by Stephens, D. J., and Hawley, E. E. The Partition of Reduced Ascorbic Acid in Blood, *J Biol Chem* **115** 653 (Oct) 1936.

15 Farmer, C. J., and Abt, A. F., cited by Stephens, D. J., and Hawley, E. E. The Partition of Reduced Ascorbic Acid in the Blood, *J Biol Chem* **115** 653 (Oct) 1936.

16 Bellows, J. Biochemistry of the Lens. V. Cevitamic Acid Content of the Blood and Urine of Subjects with Senile Cataract, *Arch Ophth* **15** 78 (Jan) 1936.

17 Farmer, C. J., and Abt, A. F. Determination of Reduced Ascorbic Acid in Small Amounts of Blood, *Proc Soc Exper Biol & Med* **34** 146 (March) 1936.

18 Ingalls, T. H., and Warren, M. Frequency of Asymptomatic Scurvy in Patients on Bland Diets, *New England J Med* **217** 443 (Sept 9) 1937.

19 Perla and Marmorston<sup>4</sup> Wilder and Wilbur<sup>10a</sup>

approximate (or minimum) average<sup>20</sup> value in normally nourished persons

Among reports in the literature on values for urinary excretion, it will suffice to refer to Youmans and his associates,<sup>21</sup> who stated that "a daily urinary excretion of 20 mg is suggested as the lower limit of normal daily excretion," and to Abbasy and his co-workers,<sup>12</sup> who asserted that "about 20 mg" is the average daily excretion of a normal adult receiving an adequate diet in England and stated that 10 to 15 mg should be considered a minimum level, below which a substandard diet may be presumed

In view of the fact, however, that ascorbic acid is excreted in some amount in the urine of every person not actually bedfast with scurvy, determinations of the presence of this substance in single specimens of urine occasionally give a far from adequate picture of the actual state of deprivation. The administration of accurately measured test doses, either intravenously or by mouth, with subsequent determination of the amount of the vitamin excreted during a measured period, has therefore been introduced as of value in establishing a diagnosis of subclinical scurvy and vitamin subnutrition of all degrees. The dose given perorally differs according to different investigators, ranging from 200 to 600 mg or more. Abbasy and his co-workers<sup>12</sup> stated that the diet may be presumed to be "unduly low in vitamin C content" if there is no response to a single test dose of 700 mg on the second day after administration. Youmans and his associates<sup>21</sup> stated that "for the present" excretion of 30 per cent of a test dose of about 600 mg by adults may be taken to indicate the lower limit of "saturation"

In the field of ophthalmology, the most fruitful work is that dealing with the general role of the vitamins in the normal and abnormal metabolism of the eye,<sup>22</sup> as there appears to exist a close interrelation between the effects of several vitamins, notably A, C and G (riboflavin), on the oxidation-reduction processes of the various structures of the eye. Buschke<sup>22a</sup> pointed out that the crystalline lens, because of its eminent suitability for research of this kind, was one of the first organs in which the water-soluble oxidation-reduction systems, vitamins C and G, glutathione and the "oxidation catalyzer," vitamin A, could be demonstrated as coexistent. A considerable amount of work has been done in connection with the presence of vitamin C in the anterior chamber

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20 Wortis, H., Wortis, S. B., and Marsh, F. I. *Rôle of Vitamin C in Metabolism of Nerve Tissue*, *Arch Neurol & Psychiat* **39** 1055 (May) 1938

21 Youmans, J. B., Corlette, M. B., Akeroyd, J. H., and Frank, H. *Studies of Vitamin C Excretion and Saturation*, *Am J M Sc* **191** 319 (March) 1936

22 (a) Buschke, W. *Die Vitamine in der Ophthalmologie*, *Ztschr f Vitaminforsch* **5** 37 (Jan) 1936 (b) Pavía, J. L., and Díez, M. *Las vitaminas A y C en oftalmología*, *Rev oto-neuro-oftal* **12** 13 (Jan) 1937

and in the lens with normal and with pathologic conditions. Of special interest in connection with the work here reported are repeated determinations of the concentration of the vitamin in eyes with cataractous conditions and with aphakia,<sup>22</sup> all results pointing to a definite reduction of the vitamin with these conditions, especially the latter, and in the amount of the reduction in the presence of cataract more or less corresponding with the degree of opacity of the lens.

Reports on attempts to apply this information clinically, however, are difficult to find. One reference to such work among American clinicians is that of treatment with vitamin C and a diet rich in glutathione of a group of patients suffering from cataracts caused by dinitrophenol,<sup>23</sup> in which "rapid improvement" was noted. One report from England<sup>24</sup> described the "very favorable reaction" of a patient with congenital cataract to administration of vitamins A and C, as measured both by reading tests and by ophthalmoscopic examination.

Since ascorbic acid therapy was begun at this institution, reprints were received of work performed in Buenos Aires, by Pavia,<sup>25</sup> on cataractous persons of advanced age. Ascorbic acid was administered both intravenously and directly into the anterior chamber of the eye, and the effects were checked by biomicrographic study of the lens. Despite the fact that some of the patients treated had suffered impairment of vision for a number of years, the percentage of improvement was gratifying (70 per cent in 10 cases). The results were much poorer in a series of 7 patients treated with subcutaneous injections only. The amounts of ascorbic acid administered in the latter instance were, however, not especially large. Of special interest is the finding that the improvement in the condition of the optic media and consequently in the visual acuity of 1 patient persisted during two months of observation after institution of treatment, despite a gradual drop of the urinary excretion values of ascorbic acid. The author concluded that this phenomenon tends to bear out other investigative work which indicates that the ascorbic acid content of the anterior chamber can remain high regardless of the level in the blood plasma.

Pavía determined the amount of ascorbic acid to be administered by titrating the amount excreted in the urine, he came to the conclusion that when this figure goes below 3 mg per hundred cubic centimeters with excretion of a normal twenty-four hour volume of urine, it is necessary to administer 300 mg of ascorbic acid daily and that when the

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23 Josephson, E. M. Ascorbic (Cevitamic) Acid in Cataract with Special Reference to Dinitrophenol Cataracts, *Science* **82** 222 (Sept 6) 1935.

24 Koepcke, G. M. Vitamins and Infections of Eye, Nose, Throat and Sinuses, *Journal-Lancet* **57** 460 (Oct) 1937.

25 Pavia, J. L. Catarata senil. Un nuevo tratamiento medico, *Rev oto-neuro-oftal* **12** 182 (July) 1937.

content exceeds 3 mg, it is necessary to give only 100 mg every other day. In Pavia's cases the duration of treatment was apparently determined entirely by the degree of improvement obtained. The author, however, did not specify the length of treatment he considered adequate definitely to determine whether any beneficial effect is to be expected.

Other references to dosage include a statement by Ingalls<sup>26</sup> to the effect that Johnson and Zilva and Hawley and his associates noted "no significant increase" in the excretion of ascorbic acid by unsaturated persons after daily administration of 200 mg for several days. He also cited van Eekelen, who required 1,800 mg for resaturation after abstaining for one month from foods containing vitamin C. There is, however, no reference to the manner in which this amount was taken nor to the time required. Youmans and others<sup>21</sup> stated that a daily dose of 25 to 100 mg, has little effect on the excretion value of unsaturated persons, and Wood<sup>26a</sup> described a patient who had frank scurvy with no ascorbic acid in the urine, who excreted 1 to 7 mg after taking a dose of 600 mg but none after that, despite a daily dose of 80 mg for one week, with clinical improvement.

#### EXPERIMENTAL STUDY

In regard to the procedure to be followed at this institution, it seemed desirable to complete all tests within one season, in view of the fact that seasonal variations in the degree of ascorbic acid saturation may be assumed with a fair degree of certainty.<sup>27</sup>

It was decided to establish as many fairly large groups of approximate values as possible before investigation of the special group of patients who presented visual disturbances. Tests on the vitamin C level in the blood were carried out also on a small group of subjects not connected with this institution but living under similar conditions. They represent a part of the nursing staff of the general hospital at Hastings, Neb. Tests on this group were performed in April and May 1938.

It proved preferable, in the interests of cooperation and because of the fact that we were dealing with patients with mental disease, to run tests on several persons simultaneously for short periods, rather than long individual tests in the determinations of urinary excretion of the vitamin. No subject was tested without a preliminary complete analysis of urine, and all persons with definitely pathologic findings were rejected. Other requisites for inclusion in the test were subjective well-being, freedom, as far as determinable, from syphilis and active tuberculosis and absence of special treatment, such as metrazol or insulin shocks or therapy with the hypertherm.

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26 Ingalls, T. H. Studies on the Urinary Excretion and Blood Concentrations of Ascorbic Acid in Infantile Scurvy, *J. Pediat.* **10** 577 (May) 1937.

26a Wood, P. A Case of Adult Scurvy, *Lancet* **2** 1405 (Dec 21) 1935.

27 Corlette, M., Youmans, J. B., Akeroyd, J., and Frank, H. A Clinical Study of Vitamin C Excretion, *South. M. J.* **29** 37 (Jan) 1937.

Participants in the tests included the members of the medical staff and their wives, the members of the nursing staff, the day and the night attendants, confined patients and patients on parole as well as various employees of other types. All of these subjects ate all meals at the institution. As far as possible, men and women were chosen in equal numbers, with the exception of the outside group, which consisted entirely of women. The tests were begun in January 1938 and continued without interruption throughout February, March, April and May. All tests on the vitamin level in the blood and in the urine preparatory to controlled administration of ascorbic acid were completed by the end of March, i.e., at a time when the values would presumably be lowest.

The urine was collected in dark brown bottles, it was acidified to contain approximately 5 per cent glacial acetic acid and was kept at or near ice box temperature. Titrations were carried out at 8 a.m., 3 p.m. and 8 p.m. The urine was examined by titration of duplicate samples with 2,6-dichlorobenzene-indophenol, the blood plasma was tested by the method of Farmer and Abt.<sup>17</sup> Blood was obtained by venipuncture, as a duplicate test, and occasionally other tests were made on each sample.

The first step in this series was a test on the twenty-four hour urinary excretion, carried out without any preparatory procedures and involving the largest number of subjects examined in any group. Some time later, twenty-four hour collections of urine were again undertaken, after the ingestion of 600 mg. of pure ascorbic acid in tablet form. The test dose was taken with breakfast, and collection of urine was started immediately, fresh fruits and fruit juices were eliminated from the diet during the period of collection, with no other change in the daily routine. In addition, the level of ascorbic acid in the blood plasma was determined, specimens of blood being taken in the morning during fasting.

The patients suspected of visual disturbances due to clouding of the media were first segregated by preliminary examination, they were then examined and grouped by a consulting ophthalmologist and were finally subjected to the tests on vitamin excretion and level in the blood just described. Before administration of ascorbic acid was begun as treatment, the series was narrowed to 12 patients, 8 women and 4 men. This number obviously represented only a fraction of the group of patients in whom difficulties of the same sort were encountered in refraction tests and in other tests at this institution. It was necessary, however, to pick subjects who could be counted on to describe their subjective impressions more or less accurately and consistently and whose mental conditions were not likely to change in the course of this investigation.

Homogeneity in every respect is not claimed for this group. All 12 persons, however, had in common subjective visual difficulties, especially in performing skilled tasks or in reading, and refraction could not be satisfactorily determined. If glasses were satisfactory when first fitted, they soon ceased to give good service. Three of the subjects, women 56, 64 and 73 years old, respectively, had well developed unilateral cataracts. One other, a woman aged 63, showed bilateral opacities of the lens, another woman, aged 47, had beginning bilateral cataracts.

For four weeks only 6 of the 12 subjects, 4 women and 2 men, received ascorbic acid. The remaining 6 served as controls in order that changes in the levels in the blood might be evaluated more accurately, as the oncoming change in seasons and the consequent change in the general diet were expected to bring about a general rise in the ascorbic acid reserves of the institutional population as a whole. Determinations of the vitamin level in the blood were carried out once a week on the subjects under treatment, except on the first subgroup for the fourth week, and on both subgroups after the fourth week. From the fourth week on, both

subgroups received ascorbic acid daily in addition to the regular diet. Small amounts of tomato juice were included as a regular fortifying feature of the diet five weeks after treatment was first begun (after one week for the second subgroup).

Treatment was begun with the administration of between 300 and 350 mg of ascorbic acid daily. This dose was reduced for short periods in some cases, depending on the level in the blood, but at the conclusion of treatment (eight weeks for the first subgroup, four weeks for the second) 11 of the 12 subjects were receiving approximately 350 mg daily. One patient did not receive any ascorbic acid during the last week of treatment. Determinations of levels in his blood plasma made during this week and those made subsequently are considered separately.

### RESULTS

In a consideration of the findings, attention is first called to the difference in the average urinary excretion of ascorbic acid among the three large institutional groups. Only the values for the "officer" group (physicians and their wives, heads of the nursing departments, etc.) actually exceeded the minimum figures considered as indicative of

TABLE 1—*Average Twenty-Four Hour Urinary Excretion of Ascorbic Acid\**

Subjects	Men and Women	Men	Women
25 officers	32.22	31.13	33.32
96 employees	14.96	16.65	14.03
Day workers	15.41		
Night workers	13.70		
31 patients†	10.94	10.64	11.22

\* Values indicate milligrams.

† Excluding those treated with ascorbic acid.

normal vitamin C nutrition, while the values for the employee group (night and day attendants, clerical employees, etc.) hovered in the main around the minimum values cited in the literature, and the excretion levels of the patient group were, with only two or three exceptions, well below these values. The exceptions in the latter group, moreover, in no case exceeded the minimum normal values (table 1).

The levels in the blood plasma represented a parallel to the findings just cited—on the whole, however, with less marked differences between the three institutional groups (table 2).

The outside group of graduate and student nurses showed levels in the blood plasma closely approximating the averages given by Bellows and others, both in March and in May, with a slightly higher average in the later determinations (table 2).

The most striking and illuminating differences were obtained in determinations of excretion after a test dose (table 3). The practically complete failure on the part of the patients to eliminate any of the test dose within twenty-four hours is the outstanding finding for these sub-



jects One woman, who lived in the same ward as other patients included in these tabulations, reflected the fact that she was receiving a high vitamin diet in the values for vitamin C after the test dose as well as, to a less complete degree, in the level in the blood plasma, but not at all in the regular urinary excretion of ascorbic acid The latter was 11.58 mg in twenty-four hours (highest value for a female patient taking the regular diet, 17.02 mg, average for both sexes, 10.94 mg) The level in the blood plasma was 1.00 mg per hundred cubic centimeters (highest value for a female patient taking the regular diet, 0.50 mg, average for both sexes, 0.49 mg) The excretion of this

TABLE 2—*Level of Ascorbic Acid\* in Blood Plasma*

Subjects	Men and Women, Average	Men, Average	Women, Average	Highest Value
13 employees	1.12	0.97	1.24	1.90
16 patients†	0.19	0.51	0.47	0.65
15 members of outside group, March 9, 1933	0.70			1.20
6 members of outside group, May 24, 1933	0.76			1.30

\* Values indicate milligrams per hundred cubic centimeters

† Excluding those treated with ascorbic acid and a patient given a special diet (see text)

TABLE 3—*Twenty-Four Hour Urinary Excretion of Ascorbic Acid\* After Test Dose*

Subjects	Men and Women, Average	Men, Average	Women, Average	Highest Value
11 employees	122.82	101.80	165.98	295.60
18 patients†	11.62	15.26	9.80	24.28

\* Values indicate milligrams

† Excluding those treated with ascorbic acid and a patient given a special diet (see text)

woman after a test dose was 226.11 mg in twenty-four hours (highest value for a female patient taking the regular diet, 16.04 mg, average for both sexes, 11.62 mg)

The lowest values throughout were obtained for the 12 patients segregated for special treatment because of visual disturbance (This grouping of patients, as of all subjects tested, was done before any tests on excretion or on level in the blood had been carried out) The second subgroup of these 12 treated subjects, however, indicated a slight general rise in the blood plasma values, apparently coincidental with the seasonal changes in diet, when tested one month later, before treatment was started (table 4)

Studies of the excretion values obtained for all groups without test doses at various times of the day indicated that the ascorbic acid appeared

to be excreted in amounts roughly corresponding to the number of hours during which individual samples were collected. A comparison of the fractional excretion values after the administration of test doses, however, revealed group differences in that the patients, who showed an apparently complete lack of saturation of vitamin C reserves, maintained about the same ratio of excretion as without the test dose, whereas the employees as a whole excreted more ascorbic acid during the seven hours from 8 a m to 3 p m, i e., immediately after ingestion of the test dose, than during the next seventeen hours, from 3 p m to 8 a m the following morning, despite a rather poor response to the test dose as compared with data given in the literature<sup>28</sup>

The fact that the accuracy of the excretion tests, especially, depended much on the cooperation both of the subjects tested and of

TABLE 4—*Average Twenty-Four Hour Urinary Excretion of Ascorbic Acid, Level in Blood Plasma and Response to Test Dose for Patients Before Treatment*

Observation	Subjects	Men and Women	Men	Women
Urinary excretion*	Subgroups 1 and 2 (12 patients)	6.35	8.02	5.50
Level in blood plasma, March 16-21, 1938†	Subgroups 1 and 2 (12 patients)	0.45	0.47	0.44
Level in blood plasma, April 23, 1938†	Subgroup 2 (6 patients)	0.55		
Response to test dose‡	Subgroups 1 and 2 (12 patients)	7.11	9.31	5.85

\* Values indicate milligrams per twenty four hours

† Values indicate milligrams per hundred cubic centimeters

‡ Values indicate milligrams

the employees aiding in the collection of specimens was considered, as a rough means of control, the amounts of urine excreted by the various groups in twenty-four hours were measured together with the amounts of ascorbic acid. The general average for all types of employees and patients, comprising about 150 subjects, was thus found to be 1,278 cc.

The values for the vitamin C content of blood plasma obtained before, during and after treatment of the special group of 12 patients are compiled in table 5. It will be noted that, apart from the initial fluctuations encountered when an attempt was made to achieve a maxi-

28 Wright, I. S., Lihenfeld, A., and MacLenathen, E. Determination of Vitamin C Saturation. A Five Hour Test After an Intravenous Test Dose, *Arch Int Med* **60** 264 (Aug.) 1937. Wortis, H., Liebmann, J., and Wortis, E. Vitamin C in the Blood, Spinal Fluid and Urine, *J. A. M. A.* **110** 1896 (June 4) 1938. Abbasy and others<sup>12</sup>. Youmans and others<sup>21</sup>.

imum rise in level in subgroup 1, the values of the blood plasma dropped to a fairly constant high level below that of the initial rise in 10 of the 12 patients, despite the fact that the daily amounts of ascorbic acid administered far exceeded the amounts required to maintain a normal

TABLE 5—*Level of Ascorbic Acid in Blood for Patients Before, During and After Treatment*

Subgroup 1													
Week of Treatment													
Case No	Patient	Sex	Age, yr	Before Treatment	First	Second	Third	Fourth	Fifth	Sixth	Seventh	Eighth	First Week After Treatment
1	M B	F	73	0.45	1.90	1.80	1.75		2.80	2.20	1.80	1.80	1.50
2	E Ba	F	61	0.44	2.80	1.90	2.20		2.50	2.55	2.25	1.80	1.55
3	M Ho	F	42	0.43	2.40	2.20	2.20		2.75	2.00	2.35	2.20	1.65
4	M H <sup>†</sup>	F	56	0.40	2.40	2.20	2.15		2.60	2.15	2.10	1.75	1.55
5	R J	M	38	0.41	1.40	1.40	1.60		2.00	1.55	1.75	1.75	1.20
6	G B	M	54	0.60	2.00	0.75	1.80		1.15	1.85	1.80	1.70	1.40
Average				0.46	2.15	1.74	1.95		2.22	2.05	2.01	1.83	1.47
Subgroup 2													
Week of Treatment													
Case No	Patient	Sex	Age, yr	Before Treatment	First	Second	Third	Fourth	First Week After Treatment				
7	E Bo	F	41	0.40				0.55	2.75	2.35	1.85	2.60	1.50
8	I H	F	47					0.50		2.20	1.75	1.40	0.80
9	H M	F	63	0.48				0.60	2.50	2.10	1.75	1.95	1.70
10	S B	F	56	0.46				0.51	1.90	1.80	1.75	1.50	(1.30)*
11	H J	M	64	0.47				0.58	2.40	2.20	1.70	(1.20)†	(0.90)†
12	J C	M	55	0.40					0.95	1.85	1.70	1.50	1.40
Average				0.44				0.55	2.06	2.08	1.75	1.67	1.36
General Average				0.45					2.15	2.07	1.88	1.76	1.40

\* Treatment continued during fifth week, not included in average

† No treatment during fourth week, not included in average

level in the blood and in the urine. That this apparent inability to maintain the maximum attainable level in the blood for more than a short period was, moreover, not due to decreased absorption in the gastrointestinal tract is indicated by the values for urinary excretion obtained for 11 of the 12 patients at the end of the eighth (fourth) week of treatment (table 6), which show a tremendous spilling over of ascorbic acid, practically equivalent, in fact, to the daily dose administered in tablet form.

The twenty-four hour urinary excretion of ascorbic acid was again tested immediately after the final manifest readings of visual acuity for this group, or about eleven days after termination of treatment. The values obtained are included in table 6. It will be noted that the patients differed little from one another in their excretion as tested at any one time, either toward the end of treatment or a fortnight later, but it may be seen also that the values obtained at the latter time are throughout equivalent only to the lower limit of normal daily excretion during a well balanced dietary regimen. That is to say, within eleven days of administration of excessive amounts of the vitamin, with evidence of high values in the blood plasma, the urine failed to show any evidence of an excess of the substance in the body. This indicates the presence of reserve depots in the body, Wortis, Wortis and Marsh<sup>20</sup> have most recently stressed the fact that certain parts of the central nervous system, as well as related structures (pituitary gland, crystalline lens and aqueous humor of the eye and adrenal glands), have been definitely found to contain relatively large amounts of ascorbic acid independent of the level in the blood.

Regardless of the date of the last tests for visual acuity all patients in the treated group were examined at the same time for reading ability and with the ophthalmoscope shortly before beginning treatment, those in subgroup 1 were reexamined after four weeks of treatment, those in subgroups 1 and 2 were examined two weeks later, again at the conclusion of the treatment and finally about eleven days after treatment had been discontinued.

Of the 12 patients thus studied, 1 man and 1 woman could not be included in a final consideration of the effects of treatment because of their psychotic condition. All of the remaining 10 showed some degree of opacity in the vitreous, and 5 showed beginning, moderately advanced or mature cataracts. Other findings were, in some instances, unusually pale disks and narrowed, somewhat tortuous retinal arteries.

Of the 5 patients primarily showing changes of the lens, 4 showed no improvement whatsoever, either of the ophthalmoscopic picture or of visual acuity as determined by manifest readings. The fifth, patient 10 (S. B., table 5), a 56 year old woman, had already undergone an operation for removal of the left lens and showed beginning cataract of the right lens. The left vitreous in particular, however, showed opacities also. Treatment apparently produced no change in the condition of the remaining lens but did affect the opacities of the vitreous, with improvement of vision in both eyes (table 7).

The remaining 5 patients showed improvement of vision (table 7), but it is worthy of note that before treatment the outstanding ophthal-

moscopic findings in these cases were changes in the fundus and in the vitreous and that the latter changes regressed under treatment to a remarkable extent, with complete clearing in some instances

Associated with these objectively determinable changes under treatment was subjective improvement of vision, expressed by such statements as these "My eyes are stronger" "I can do my needle work without my glasses now", "I can read much easier", "Things seem so much clearer than they did" Moreover, both objective and subjective improvement set in rapidly when it occurred at all and in most cases did

TABLE 6—*Twenty-Four Hour Urinary Excretion of Ascorbic Acid\* for Patients During and After Treatment*

Time of Determination	Average	Highest Value
Last week of treatment	323.21	356.13
11 days after treatment	16.70	28.55

\* Values indicate milligrams

TABLE 7—*Manifest Readings of Visual Acuity for Patients Treated Before, During and After Treatment\**

Case No †	Patient	Sex	Age, Yr	March 15	April 19 or Later	May 31
4	M Ha	F	56	O D 20/70 O S 20/70	O D 20/40 O S 20/40	O D 20/40+2 O S 20/40
6	G B	M	51	O D 20/60 O S 20/70	O D 20/60 O S 20/50	O D 20/260 O S 20/50
7	E Bo	F	41	O D 20/70 O S 20/50-1	O D ‡ 20/10-1 O S 20/10-2	O D 20/30-2 O S 20/30-2
10	S B	F	56	O D 20/70+2 O S 20/60	O D ‡ 20/10-2 O S 20/200+1	O D 20/50+1 O S 20/100-1
11	H J	M	64	O D 20/200 O S 20/200	O D ‡ 20/100+1 O S 20/200+2	O D 20/70 O S 20/70-1
12	J O	M	55	O D ? O S ?	O D § 20/40+2 O S 20/30-2	O D 20/30-1 O S 20/30

\* One test not included

† Numbers same as in table 5

‡ Tested May 7

§ Tested May 15

not progress much after two weeks of daily treatment. The last examination, made about eleven days after completion of several weeks of treatment, showed only occasional further changes of note.

As the 2 patients eliminated from this series were originally included in subgroup 1, only 4 subjects in this subgroup were actually considered in these comparisons. Of these, 2, or 50 per cent, reacted favorably to treatment. In subgroup 2, 4 of 6, or 66 per cent, reacted favorably to treatment. This subgroup received only half as much ascorbic acid as subgroup 1, the patients were distributed within the two subgroups as evenly as possible in regard to both age and ophthalmologic findings.

A comparison of the average ages of the patients whose vision improved with those in whom it was unimproved indicates that the older the person, the less favorable the reaction, as the subjects whose condition improved showed an average age of 54.3 years, as against 61.8 years for those whose status remained unimproved. It should be noted, however, that among the most strikingly benefited persons was a patient 64 years old.

All patients were questioned at regular intervals concerning the general state of appetite, sleep, elimination, etc. In the majority of cases the responses were favorable, in some cases remarkably so, especially in regard to mood and appetite. One patient in particular (patient 11, H. J., table 5), a 64 year old man, suffered severely from pains in all large joints and in the spine, with marked initial stiffness on arising from bed or after sitting in one position for any length of time. After the first week of treatment this patient spontaneously offered the information that the initial stiffness had diminished considerably and that the pains in the joints were definitely less troublesome. Throughout the remainder of the treatment and subsequently he has repeatedly made the statement that he feels "better in every way than for the past two years." This feeling of general well-being can probably be ascribed in great part simply to the relief from the constant articular pains. This effect of the administration of ascorbic acid seems, moreover, to be in accordance with recent reports on the manifestations of various degrees of vitamin C deficiency.<sup>29</sup>

It was observed also that in determination of the vitamin levels in the blood plasma the punctured veins, which had, especially in the older members of the group, shown a tendency to bleed rather profusely after venipuncture, gradually improved in this respect to a remarkable degree.

Four of the 12 patients comprising the treated group were inmates of epileptic wards and were receiving either phenobarbital or phenobarbital and bromides at the time this investigation was carried out. The medication apparently had no effect on the reaction to ascorbic acid, for the number and character of the seizures experienced by these patients in the course of the year revealed no demonstrable change during ascorbic acid therapy.

#### SUMMARY

Various groups of the employee and patient population of the Hastings State Hospital were tested for the twenty-four hour urinary excretion of ascorbic acid, the level of the substance in the blood

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<sup>29</sup> Rinehart, J. F., Greenberg, L. D., Baker, F., Mettier, S. R., Bruckman, F., and Choy, F. Metabolism of Vitamin C in Rheumatoid Arthritis, *Arch. Int. Med.* **61**: 537 (April) 1938. Booth and Hansen.<sup>10b</sup>

plasma and the twenty-four hour excretion after a peroral test dose of 600 mg of pure ascorbic acid in tablet form. The tests were all carried out during the late winter months of 1938. The findings differed among the different groups, they indicated definite vitamin C deficiency for the patients in general.

For a control group of persons not connected with the institution the levels in the blood plasma were determined in March and May 1938, the test at the latter time coinciding with termination of treatment at this institution. The findings corresponded in the main with those given in the literature for normally nourished subjects.

All the described tests were performed also on a special group of patients who presented visual disturbances due apparently to changes in the tissues associated with aging of the eye. These patients were subjected, in addition, to ophthalmoscopic examination and to reading tests. The findings indicated an even more marked vitamin C deficiency in this group than among the other institutional patients.

The special group was divided into two subgroups, one of which received massive daily doses of ascorbic acid by mouth for eight weeks, while the other received the same medication for four weeks.

Determinations of the levels of reduced ascorbic acid in the blood plasma were carried out at regular intervals during treatment and one week after it, in addition to ophthalmoscopic and reading tests. The twenty-four hour urinary excretion was determined during the last week of treatment and again two weeks later, immediately after the final examination for visual acuity. The findings indicated improvement of eyesight in all patients not suffering primarily from senile cataract. The general well-being of the patients under treatment appeared to be beneficially affected as well.

All findings are recorded in tabular form and briefly discussed, with mention of incidental observations not directly related to the problem under consideration. Sixty per cent of the treated group as a whole showed improvement, as measured by reading test, ophthalmoscopic examination and the subjective reactions of the patients. The results indicated, moreover, that marked improvement sets in within the first two weeks of treatment, if it occurs at all, with slow progression or no further change from then on. Cataracts were apparently not affected by this method of treatment, all improvements being due to clearing of the other optic media and apparently even to some degree to a beneficial effect on the retinal vessels and the head of the optic nerve (or the optic nerve as a whole?). Whether the latter findings represented a direct or an indirect action of ascorbic acid is still a matter of conjecture, although reports of recent work indicate that a direct effect is probable.<sup>20</sup>

## CONCLUSIONS

From a comparison of the excietion values and the levels in the blood during and after treatment as well as from the results of ophthalmoscopic and reading tests, it appears that ascorbic acid deficiency can be held at least partly responsible for impairment of vision associated with senescence of the human eye and that the administration of ascorbic acid by mouth in adequate doses can counteract this process, so far as the crystalline lens is not primarily involved

The lens, although showing a definitely subnormal ascorbic acid content with cataractous conditions, apparently cannot be favorably affected by the administration of ascorbic acid by mouth, even in excessive amounts, after senile changes have set in

The findings here reported also indicated that little is gained by continuing the administration of large amounts of ascorbic acid if there is no measurable improvement after daily treatment for two weeks. This time limit is liberal

The fact has not been lost sight of that a method of treatment properly combining more than one of the vitamins known to be specifically associated with the metabolic functioning of the eye may prove successful when ascorbic acid alone ceases to be of benefit

The Henry Ford Hospital

All manifest readings of visual acuity were carried out by Dr D M Judkins-Davies, of the medical staff of Hastings State Hospital, who first suggested a possible connection between vitamin deficiency and the condition of the optic media of the patients at this institution and who was in close cooperation with me during the testing of the various groups

Dr E C Foote, of the Foote Clinic, Hastings, Neb, was ophthalmologic consultant

The ascorbic acid used in these tests was furnished by the Department of Clinical Research of the Abbott Laboratories, North Chicago, Ill



# EFFECT OF BREATHING GASES UNDER POSITIVE PRESSURE ON LUMENS OF SMALL AND MEDIUM-SIZED BRONCHI

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AND

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A constriction in any part of the air passages from the glottis to the alveoli causes an additional resistance to the passage of air. This results in an increased effort on the part of the respiratory musculature to ventilate the lungs. When obstruction is present within the thorax, respiration modifies the degree of obstruction, since the lumens of the bronchi enlarge on inspiration and constrict during expiration.<sup>1</sup> This variation in size of the smaller bronchi has been demonstrated by roentgenograms of the lungs, made after injection of iodized poppyseed oil.<sup>2</sup> In the extrathoracic trachea and larynx, however, the lumen is not exposed to varying intrathoracic pressures, it is, moreover, protected from alteration in its size by strong cartilaginous rings.

In asthmatic dyspnea, inspiration is short and forcible, and expiration is prolonged. The long-drawn-out character of expiration may be explained by the constriction of the bronchi during the expiratory cycle, a powerful expiratory effort might produce an even greater narrowing of the smaller bronchi and further delay the egress of air. In previous reports of one of us therapy by inhalation under positive pressure of 2 to 7 cm. of water has been described in the treatment of severe asthma and acute pulmonary edema.<sup>3</sup> In obstructive dyspnea the intrapleural

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From the Department of Medicine and the Department of Roentgenology, College of Physicians and Surgeons, Columbia University, and the Presbyterian Hospital.

1 Jackson, C., and Jackson, C. L. *Bronchoscopy, Esophagoscopy and Gastroscopy. A Manual of Peroral Endoscopy and Laryngeal Surgery*, ed. 3, Philadelphia, W. B. Saunders Company, 1934.

2 Macklin, C. C. The Dynamic Bronchial Tree, *Am. Rev. Tuberc.* **25**: 393 (March) 1932.

3 Barach, A. L. (a) The Therapeutic Use of Helium, *J. A. M. A.* **107**: 1273 (Oct. 17) 1936, (b) Recent Advances in Inhalation Therapy in the Treatment of Cardiac and Respiratory Disease. Principles and Methods, New York State J. Med. **37**: 1095 (June 15) 1937. (c) Kernan, J. D., and Barach, A. L. Role of Helium in Cases of Obstructive Lesions in the Trachea and Larynx, *Arch. Otolaryng.* **26**: 419 (Oct.) 1937. (d) Barach, A. L., Martin, J. D., and Eckman, M. Positive Pressure in the Treatment of Pulmonary Edema, *Ann. Int. Med.* **12**: 754 (Dec.) 1938.

negative pressure is increased during the inspiratory cycle. When air, oxygen or a mixture of helium and oxygen is breathed under a positive pressure of approximately 5 cm of water, the pathologically elevated negative pressure within the chest is diminished, and dyspnea is alleviated.

During the expiratory cycle the employment of positive pressure appeared to have the advantage of an internal distending force within the tubules of the respiratory passageway, which tended to diminish their constriction during expiration. Evidence for this belief was found in the behavior of patients with continuous asthmatic dyspnea of mild or moderate degree. Breathing under a positive pressure of 2 to 5 cm of water frequently resulted in a disappearance of many of the rales heard during expiration and in subjective relief. Patients who were taught to purse their lips during expiration, thus creating a pressure which was reflected backward into the lungs, often observed a clearing of the wheezing sounds previously heard. This might in part

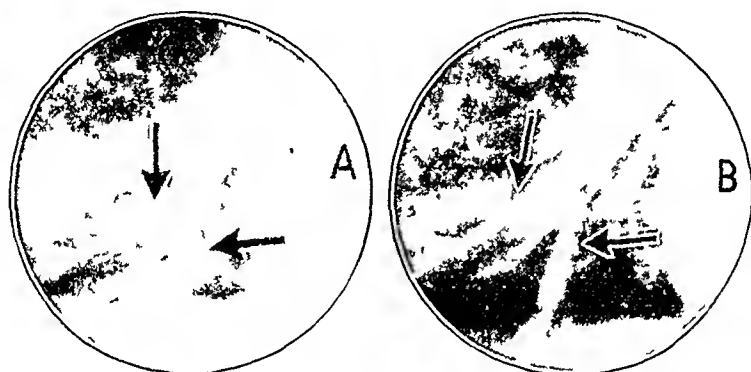


Fig 1—*A*, a branch of the bronchial tree after injection of iodized poppyseed oil at the end of inspiration. *B*, a branch of the bronchial tree after injection of iodized poppyseed oil at the end of expiration.

have been due to a decrease in the velocity of air. It seemed desirable, therefore, to test the hypothesis that positive pressure accomplished a relative increase in the diameters of the smaller bronchi during the expiratory cycle, since, if this were true, it would make for more uniform and efficient emptying of the alveoli.

#### METHODS

Seven patients with varying degrees of asthmatic dyspnea were given intra-tracheal injections of iodized poppyseed oil. Roentgenograms of the chest were taken at the end of inspiration and of expiration, before and during the inhalation of air under a positive pressure. The apparatus consisted of a motor blower unit, a 1 inch (2.5 cm) rubber tube, a T tube which made connection to the patient by means of a mouthpiece and a second rubber tube, which led from the patient into a water bottle. The distance to which the expiratory tube was immersed in water represented the pressure obtained during expiration. The pressure used was 5 cm of water at the end of inspiration and 8 cm at the end of expiration.

## RESULTS

The effect of inspiration and expiration on the size of a branch of the bronchial tree during an attack of asthma of moderate degree is shown in figure 1. Comparison of the widths of the bronchi to which the arrows point reveals a distinct narrowing during the expiratory cycle.

In the 7 patients in whom the effect of positive pressure was studied no consistent changes were observed at the end of inspiration. In 2, the diameters of the bronchi appeared larger when positive pressure was used at the end of inspiration. However, at the end of expiration the widths of the branches of the bronchial tree studied roentgenographically showed a consistent increase when positive pressure was employed. In figure 2 a comparison of the results obtained in a patient with asthma at the end of expiration with and without positive pressure may be seen. It will be observed that the smaller bronchi showed an enlargement of 1 mm in diameter and the moderate-sized bronchi 2 mm in diameter when expiration was conducted under positive pressure.

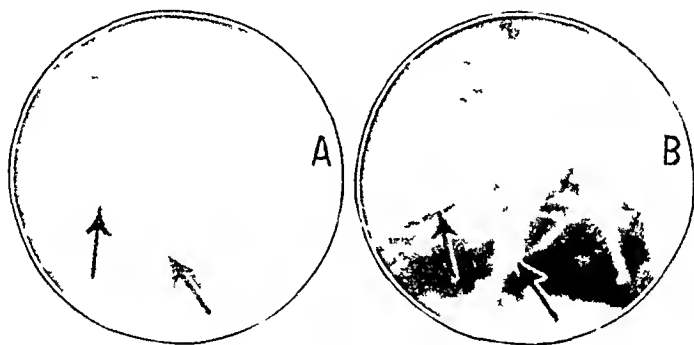


Fig 2—*A*, a branch of the bronchial tree after injection of iodized poppyseed oil at the end of expiration with the patient breathing air without pressure. *B*, a branch of the bronchial tree after injection of iodized poppyseed oil at the end of expiration with the patient breathing air under positive pressure.

## CONCLUSIONS

The effect of breathing air under positive pressure on the size of a branch of the bronchial tree was studied by means of roentgenograms of the chest after injection of iodized poppyseed oil in a series of 7 patients during an attack of mild or moderate asthma. The widths of the small and the moderate-sized bronchi were approximately 1 to 2 mm larger at the end of expiration when positive pressure was used.

These studies appear to confirm previously reported evidence that breathing atmospheres under positive pressure possesses the physiologic advantage of maintaining a larger bronchial lumen, especially during the expiratory cycle, and thus promoting a more efficient emptying of the alveoli of the lungs.

# MANIFESTATIONS OF TRICHINIASIS IN THE CENTRAL NERVOUS SYSTEM

## REPORT OF A CASE WITH LARVAE IN THE SPINAL FLUID

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Trichiniasis has been known to involve the central nervous system since 1906, when Frothingham<sup>1</sup> first demonstrated the larvae of *Trichinella spiralis* in a human brain. Since that time 24 cases have been reported in which the central nervous system has been definitely involved. In spite of this ever increasing evidence, the fact that the larvae do invade the central nervous system and cause symptoms is not generally appreciated. Textbooks rarely mention it.

Recently I had the privilege of observing and following a case of encephalitis due to trichiniasis, with recovery. Larvae were isolated from the spinal fluid. This case is reported in detail, with a brief review of the literature.

### REPORT OF CASE

*History*—L T, a white man aged 25 years, was admitted to the contagious division of the University Hospital on April 4, 1938, in a comatose state. The history, as obtained from relatives, was that the patient had been apparently well until about March 20, 1938, at which time he noted fatigue, drowsiness and "rheumatism" in the right arm. A day or so later a rash developed on both forearms, described as being made up of small red spots surrounded by larger red blotches about 1 cm in diameter. The rash disappeared several days after the application of a lotion. Although the patient was drowsy and slept at every opportunity, he continued his daily occupation of feed grinding in a rural community.

On April 2, 1938, ten days after the onset of fatigue and drowsiness, he was observed to have a staggering gait and to stumble over chairs when he walked about the house. He slept most of that day and by evening was incontinent of urine and of feces. He could be aroused only with great difficulty. On the following day he did not respond to environmental stimuli, which included loud calls, given in an attempt to arouse him. He entered the hospital in this condition.

There was no history of chills, fever, nausea, vomiting or diarrhea. There was no puffiness of the eyelids or injection of the conjunctiva. There were no convulsions.

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From the contagious division of the Department of Pediatrics and Infectious Diseases of University Hospital.

1 Frothingham, C. A Contribution to the Knowledge of the Lesions Caused by *Trichina Spiralis* in Man, J M Research **15** 483-490 (Dec ) 1906

Within two weeks after his admission to the hospital, the patient's mental state had improved sufficiently for him to give coherent answers to questions. With considerable interrogation the following information was obtained. Three or four days prior to the development of the "rheumatism" in the right arm, the patient had purchased half a pound of sausage and had eaten it uncooked. None of it was taken home to the rest of the family. He vaguely remembered the rash on the forearms, but beyond that all was confusion until he regained complete consciousness three weeks later.

*Physical Examination*—The patient was well developed and well nourished. He was in a comatose state. Though he did not respond to questions, he did react to painful stimuli by reflex defense movements. There was no respiratory distress or cyanosis. The rectal temperature was 99 F, the respiratory rate 18 and the pulse rate 80. The skin was dry and of normal color, and there were no eruptions. There was no edema of the eyelids. The pupils were widely dilated, regular and equal, they reacted sluggishly to light. There was transient divergent strabismus. Fundusoscopic examination of the right eye revealed the disk and the surrounding retina to be edematous, with a crescentic patch of exudate about 3 mm long just above and temporal to the disk. There was a slight perivascular change along the superior temporal vein. There were no hemorrhages. Fundusoscopic examination of the left eye showed slight edema of the disk and of the surrounding retina but no hemorrhages or exudates.

The ears and the nose were normal. There was poor oral hygiene and the pharynx was mildly injected. There was no rigidity of the neck. The heart and the lungs were normal. The blood pressure was 105 systolic and 80 diastolic. There was no edema or deformity of the extremities. The upper extremities presented definite rigidity on the right, with some increase of muscle tone on the left, the deep reflexes were equal and active. The abdominal and the cremasteric reflexes were present and equal. The lower extremities showed no disturbance of muscle tone and no weakness. The knee jerk reflexes were present and equal. The Achilles tendon reflexes were increased with bilateral ankle clonus, exhaustible on the left and inexhaustible on the right. There was a definite Babinski reflex on the right, a less definite one on the left. The patient reacted to painful stimuli over the entire body.

*Initial Laboratory Observations*—Examination of the urine gave results entirely negative. Examination of the blood on April 5, 1938, revealed hemoglobin, 95 per cent, red cells, 4,980,000, and white cells, 7,800, with polymorphonuclears 50 per cent, eosinophils 38 per cent, lymphocytes 12 per cent, and monocytes and basophils, none. The Kahn test of the blood was negative. The sugar content of the blood was 78 mg and the nonprotein nitrogen content 42 mg per hundred cubic centimeters.

Lumbar puncture on admission yielded a clear, colorless fluid under normal pressure. The cell count was 10 lymphocytes per cubic millimeter. The Pandy test was negative. The sodium chloride content was 686 mg and the sugar content 55 mg per hundred cubic centimeters. The colloidal gold and the Kahn test were negative. Repeated examinations of the stools showed nothing of importance.

*Course*—Owing to the comatose condition of the patient, he was restrained and given intravenous fluids for several days. Three days after his admission to the hospital he was beginning to respond. His eyes would follow a light, and he would nod or shake his head in response to questions. Ten days after admission he was able, with difficulty, to carry on a conversation, and at this time he told of having eaten raw sausage. On two occasions urine pooled from the specimens

of three days failed to show any lead, arsenic or mercury. Biopsies of the right deltoid and the right biceps muscle, taken on April 15 and on April 19, respectively, showed patchy and active chronic myositis. There was necrosis of scattered muscle fibers with adjacent lymphoid infiltrations. Eosinophilic leukocytes were present in moderate numbers. No free or encysted larvae were found. On April 7 and 14 cutaneous tests with trichina antigen, using 0.1 cc. of a 1:10,000 solution, were negative.

Lumbar punctures were repeated on April 27 and April 28. The physical and chemical findings were essentially the same as those recorded on admission. These later specimens, however, were centrifuged. Two sluggishly motile larvae of *T. spiralis* were isolated from the fluid drawn on April 27 and one actively motile larva from that obtained on April 28. Hanging drop preparations were made, and microscopic moving pictures were taken of the motile larvae.

The patient's general condition steadily improved. At the time of discharge, on April 30, he was alert and mentally clear. However, he did not have normal control over his arms and legs, and his writing was scarcely legible. The right

*Results of Examinations of the Blood in a Case of Encephalitis Due to Trichiniasis*

Date	Hemo globin, per Cent	Red Blood Cells, per Cu. Mm.	White Blood Cells, per Cu. Mm.	Poly- morpho- nuclears, per Cent	Baso- phils, per Cent	Eosino- phils, per Cent	Lympho- cytes, per Cent	Mono- cytes, per Cent
4/ 5/38	95	4,980,000	7,800	50	0	38	12	0
4/ 7/38	88	4,600,000	8,800	37	0	45	15	3
4/ 9/38				43	0	45	10	2
4/11/38			10,800	56	0	32	10	2
4/13/38	97		8,100	57	0	30	13	0
4/18/38			7,200	56	1	28	14	1
4/20/38	94		8,400	60	2	27	10	1
4/29/38			9,750	55	0	17	24	4

ankle clonus and the positive right Babinski reflex were still present. Both retinas still showed mild edema. On the right there were exudates and a few vitreous opacities.

The accompanying table gives a detailed account of observations on the blood from time to time throughout the patient's stay in the hospital.

#### NEUROPATHOLOGY

Those changes due to the presence of the larvae of *T. spiralis* in the brain have been designated as inflammatory, while those due to toxins have been designated as nonspecific. The latter changes are considered the more dangerous and are more common.

The larvae of *T. spiralis* have been microscopically demonstrated in the brain by Frothingham,<sup>1</sup> Salzer,<sup>2</sup> Hassin and Diamond,<sup>3</sup> Gruber

<sup>2</sup> Salzer, B. F. Trichinosis. Study of an Epidemic of Fourteen Cases of Trichinosis with Cures by Serum Therapy, *J. A. M. A.* **67**: 579-580 (Aug. 19) 1916.

<sup>3</sup> Hassin, G. B., and Diamond, I. B. Trichinosis Encephalitis. A Pathologic Study, *Arch. Neurol. & Psychiat.* **15**: 34-47 (Jan.) 1926.

and Gampei,<sup>4</sup> Pund and Mosteller<sup>5</sup> and Most and Abeles<sup>6</sup> Portions of the larvae have been demonstrated in the retina by von Herrenschiwand<sup>7</sup> In these cases the brain was usually diffusely congested with punctate hyperemia The cortex, the basal ganglia, the medulla and the cerebellum contained minute inflammatory foci or nodules usually made up of glia cells, plasma cells, lymphocytes and polymorphonuclear leukocytes, with an occasional endothelial leukocyte In these nodules the granular parasites were usually found Nonspecific degenerative changes were also occasionally present

Cases showing only nonspecific degenerative changes, similar to those seen in patients dying of severe systemic infections, such as typhoid fever and malaria, have been reported by Knorr,<sup>8</sup> Bloch and Hassin,<sup>9</sup> Pavlica,<sup>10</sup> Walker,<sup>11</sup> Filinski<sup>12</sup> and Gordon and his associates<sup>13</sup> Hassin and Diamond,<sup>3</sup> who observed microscopically the larvae as well as the nonspecific changes, concluded that the latter are due to the combined action of the toxins from the decomposed muscles and the catabolic products of the larvae They described these changes as being areas of focal encephalomalacia in which are found neuronophagia, satellitosis and an accumulation of lipoids Bloch and Hassin<sup>9</sup> found the most striking feature in their case to be vacuolation of the tissues of the brain, caused mainly by the enlargement of the perivascular spaces

Von Herrenschiwand<sup>7</sup> reported a case in which the larvae were found in the retina on autopsy Characteristic accumulations of cells were found along the periphery, mainly in the region of the ora serrata The

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4 Gruber, G B, and Gamper, E Ueber Gehirnveränderungen bei menschlicher Trichinose, Verhandl d deutsch path Gesellsch **22** 219-221, 1927

5 Pund, E R, and Mosteller, R Trichinosis Demonstration of the Parasites in the Brain, J A M A **102** 1220-1222 (April 14) 1934

6 Most, H, and Abeles, M Trichiniasis Involving the Nervous System, Arch Neurol & Psychiat **37** 589-616 (March) 1937

7 von Herrenschiwand, F Ueber die Beteiligung des Augapfels an der Trichinellen-Einwanderung bei menschlicher Trichinose, Arch f Ophth **119** 374-385, 1927

8 Knorr, H Beitrag zur Kenntnis der Trichinellenkrankheit des Menschen, Deutsches Arch f klin Med **108** 137-159 (Sept 30) 1912

9 Bloch, L, and Hassin, G B Trichinosis Complicated by Encephalitis, M Rec **91** 537-540 (March 31) 1917

10 Pavlica, F Pathologisch-anatomisches Bild der kleinen Trichinoseepidemie in Mahren im Jahre 1925, Med Klin **23** 167-169 (Feb 4) 1927

11 Walker, A T Trichiniasis Report of an Outbreak Caused by Eating Trichinous Bear Meat in the Form of "Jerky," J A M A **98** 2051-2053 (June 11) 1931

12 Filinski, W Pathologic Changes in the Central Nervous System in Trichinosis, Polskie arch med wewn **10** 451-457, 1932

13 Gordon, M B, Cares, R, and Kaufman, B Encephalitis and Myocarditis in a Fatal Case of Trichinosis Report of a Case in a Fourteen-Year-Old Girl, J Pediat **6** 667-675 (May) 1935

accumulations were made up essentially of proliferating cells of the capillary walls. There was some hyalinization, and the capillaries were dilated. An inflammatory infiltrate of lymphocytes and polymorphonuclear neutrophils was also noted. Ten such accumulations were examined, and larvae of *T. spiralis* were found in six of them.

#### CLINICAL MANIFESTATIONS

Fifteen cases of trichiniasis producing encephalitis or encephalomyelitis with delirium, stupor or coma and neurologic signs indicating a diffuse involvement of the brain and occasionally of the spinal cord have been reported.<sup>14</sup>

Meningitis due to trichiniasis has been reported by Glazier,<sup>15</sup> Gaisbock,<sup>16</sup> Bloch,<sup>17</sup> Van Cott and Lintz,<sup>18</sup> Meyer,<sup>19</sup> Chasanow,<sup>14e</sup> MacDonald and Waddell<sup>20</sup> and Spink and Augustine.<sup>21</sup> Larvae of *T. spiralis* were isolated from the spinal fluid in some of these cases, in others they were not.

Loss of deep reflexes has frequently been observed in trichiniasis. Merritt and Rosenbaum<sup>14m</sup> reviewed a series of 110 cases in which treatment for trichiniasis had been given at the Boston City Hospital.

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14 (a) Bloch and Hassin<sup>9</sup> (b) Sterling, W. Les troubles nerveux de la trichinose, *Rev. neurol.* **1** 435-439 (April) 1925. (c) Hassin and Diamond<sup>3</sup> (d) Gruber and Gamper<sup>4</sup> (e) Chasanow, M. Meningitis bei Trichinose, *Deutsche Ztschr. f. Nervenheilk.* **103** 197-205, 1928. (f) Salan, J., and Schwartz, B. Trichinosis with Involvement of the Central Nervous System, *J. A. M. A.* **90** 611 (Feb. 25) 1928. (g) Horlick, S. S., and Bicknell, R. E. Trichinosis with Widespread Infestation of Many Tissues, *New England J. Med.* **201** 816-819 (Oct. 24) 1929. (h) Pund and Mosteller<sup>5</sup> (i) Walker<sup>11</sup> (j) Filinski<sup>12</sup> (k) Gordon, Cares and Kaufman<sup>13</sup> (l) Spink, W. W. Cardiovascular Complications of Trichinosis, *Arch. Int. Med.* **56** 238-249 (Aug.) 1935. (m) Merritt, H. H., and Rosenbaum, M. Involvement of the Nervous System in Trichiniasis, *J. A. M. A.* **106** 1646-1649 (May 9) 1936. (n) Most and Abeles<sup>6</sup>

15 Glazier, W. C. W. Report on Trichinae and Trichinosis, Document 84, United States Treasury Department, Marine-Hospital Service, 1881.

16 Gaisbock, F. Beobachtungen über Trichinose, *Wien. klin. Wchnschr.* **22** 410-414, 1909.

17 Bloch, L. Trichinosis. Report of a Case with the Trichinae Larvae in the Spinal Fluid, *J. A. M. A.* **65** 2140-2141 (Dec. 18) 1915.

18 Van Cott, J. M., and Lintz, W. Trichinosis, *J. A. M. A.* **62** 680-684 (Feb. 28) 1914.

19 Meyer, J. Trichinosis. A Report of Three Cases Simulating Meningitis, with the Findings of Trichinae Larvae in the Spinal Fluid, *J. A. M. A.* **70** 588-591 (March 2) 1918.

20 MacDonald, E. P., and Waddell, K. C. An Epidemic of Trichinosis, *J. A. M. A.* **92** 449-453 (Feb. 9) 1929.

21 Spink, W. W., and Augustine, D. L. The Diagnosis of Trichinosis, with Especial Reference to Skin and Precipitin Tests, *J. A. M. A.* **104** 1801-1805 (May 18) 1935.



over a twenty year period. Absence of deep reflexes was noted in 10 per cent of the cases. Chasanow<sup>14e</sup> considered the loss of reflexes in trichiniasis to be caused by actual neuritis. However, Most and Abeles<sup>9</sup> recently reported a case in which there was absence of deep reflexes, and at autopsy there was no evidence of degeneration of the peripheral nerves. They concluded that the loss of reflexes was in some way due to the pathologic changes in the muscles.

Neuroretinitis due to trichiniasis has been reported by several observers. Parker<sup>22</sup> described a case in which there was diffuse edema of both retinas. The retinal veins were full and tortuous, and several small hemorrhages were seen. He considered these changes to be due to an acute toxic state similar to that present in acute nephritis. Salan and Schwartz<sup>11f</sup> reported a case of optic neuritis in which the larvae were found in the spinal fluid. Spink<sup>11i</sup> described a retinal hemorrhage associated with trichiniasis. Diplopia in cases of trichiniasis has been reported by Parker,<sup>22</sup> Sicard<sup>23</sup> and Stoll.<sup>24</sup> Dilatation of the pupils has been noted late in the disease by Glazier,<sup>15</sup> von Herrenschwand,<sup>7</sup> and Van Cott and Lintz.<sup>16</sup>

#### LARVAE IN THE CEREBROSPINAL FLUID

Larvae of *T. spiralis* were first isolated from the spinal fluid by Van Cott and Lintz<sup>16</sup> in 1914. Larvae have subsequently been found in the spinal fluid of patients with manifestations of involvement of the central nervous system by Salan and Schwartz,<sup>11f</sup> MacDonald and Waddell,<sup>20</sup> Salzer,<sup>2</sup> Horlick and Bicknell<sup>11e</sup> (autopsy), Meyer,<sup>19</sup> Hassin and Diamond,<sup>3</sup> Prym<sup>25</sup> and von Herrenschwand<sup>7</sup> (autopsy).

Cases in which larvae have been isolated from the spinal fluid in the absence of neurologic signs have been reported by Bloch,<sup>26</sup> Preble,<sup>27</sup> Elliott,<sup>28</sup> Cummins and Carson<sup>29</sup> and Lintz.<sup>30</sup>

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22 Parker, F. J. The Eye Symptoms of Sporadic Trichinosis, with Report of Cases, *M. Rec.* **72** 179-181, 1907.

23 Sicard, M. H. Trichinosis, with a Report of Cases, *M. Rec.* **86** 282-285 (Aug. 15) 1914.

24 Stoll, H. F. Trichinosis. Report of Two Cases Presenting Diplopia and One, Polyserositis, *J. A. M. A.* **92** 791-793 (March 9) 1929.

25 Prym, P. Ueber Trichinose beim Menschen, *Centralbl. f. allg. Path. u. path. Anat.* **34** 89-94 (Oct. 15) 1923.

26 Bloch, L. Report of a Series of Cases of Trichinosis with Remarks on Diagnosis, *Illinois M. J.* **29** 369-373 (May) 1916.

27 Preble, R. A Case of Trichinosis. Trichinae Demonstrated in the Spinal Fluid, *M. Clin., Chicago* **1** 1163-1171 (May) 1916.

28 Elliott, A. R. Trichinosis. Report of a Case with Trichinae Larvae in the Spinal Fluid, *J. A. M. A.* **66** 504-505 (Feb. 12) 1916.

29 Cummins, W. T., and Carson, G. R. A Case of Trichinosis with Embryo in the Spinal Fluid, *J. A. M. A.* **66** 1856-1857 (June 10) 1916.

30 Lintz, W. Trichinosis and the Cerebrospinal Fluid, *J. A. M. A.* **66** 1856 (June 10) 1916.

A total of 24 cases have been reported in which larvae of *T. spiralis* have been isolated from the spinal fluid. In 11 of these the patient recovered, and in 4 the patient died during the acute stage of the disease. In 9 cases no report was made as to the final outcome.

The spinal fluid occasionally is under increased pressure. Lymphocytes are usually present, varying in number from 10 to 240 per cubic millimeter. The results of other laboratory examinations of the fluid are usually negative.

Oddly enough there seems to be no definite relation between the presence of larvae in the spinal fluid and the symptoms or signs of involvement of the central nervous system. In the case reported in this paper the larvae were isolated from the spinal fluid during the sixth



Photomicrograph of a trichina larva isolated from the spinal fluid

week of the disease. There had never been any meningeal signs, and at that time the encephalitic signs had cleared about 75 per cent. In the case reported by Cummins and Carson<sup>29</sup> the larva was isolated from the spinal fluid during the fifth week of the disease. No symptoms of involvement of the central nervous system had been present at any time. Salzer reported a case of a 3 year old girl in which larvae of *T. spiralis* were found in the spinal fluid three months after clinical recovery.

From these observations it seems logical to infer that the larvae are present in most cases of trichiniasis regardless of the presence or absence of neurologic signs. It might be well to examine a centrifuged specimen of spinal fluid in all cases suspected of being instances of trichiniasis before a biopsy of muscular tissue is made. Lumbar puncture is less complicated, more economical and usually less objectionable to the patient than the biopsy.

## COMMENT

The case reported in this paper presents certain features of special interest. The clinical picture at the time of the patient's admission to the hospital was that of toxic encephalitis with neuroretinitis. There were no gastrointestinal symptoms, and no history of edema of the eyelids could be obtained. The temperature was normal throughout the entire course of the disease. Fever is usually so much a part of the picture that trichiniasis and typhoid are frequently confused.

Dilatation of the pupils, mentioned by previous observers, was noted in this case. On the patient's admission to the hospital this feature was so pronounced that I thought he had received atropine drops in the eyes before coming to the hospital.

The eruption on the forearms may or may not have been related to the trichiniasis. Tyzzer<sup>31</sup> stated that a transient scarlatiniform rash is sometimes seen. Elliott<sup>28</sup> reported a case in which "rose spots" were noted on the abdomen.

The larvae were isolated from the spinal fluid during the sixth week of the disease, after most of the symptoms and signs had disappeared. Microscopic moving pictures of these motile larvae, taken by Dr. Harry A. Towsley, demonstrate great activity.

## SUMMARY

A case of trichiniasis which presented a clinical picture of toxic encephalitis and neuroretinitis, with subsequent recovery, is reported. Motile larvae were isolated from the spinal fluid after the encephalitic signs had largely disappeared.

Review of the literature reveals that the presence of larvae in the spinal fluid does not always produce clinical manifestations of involvement of the nervous system. Larvae of *T. spiralis* in the spinal fluid have been reported in 24 cases. Of these, 4 were fatal, a mortality rate of 26.6 per cent.

From the reported cases it seems probable that careful examination of the spinal fluid in suspected cases of trichiniasis, with or without symptoms of involvement of the central nervous system, may aid in the diagnosis of this disease.

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31 Tyzzer, E. E., in Cecil, R. Textbook of Medicine, Philadelphia, W. B. Saunders Company, 1937, pp. 454-456.

# SULFANILAMIDE

## A STUDY OF ITS MODE OF ACTION ON HEMOLYTIC STREPTOCOCCI

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In previous studies of the streptococidal power of whole blood *in vitro*, it was ascertained that the organisms were killed by intracellular digestion following phagocytosis. In order to render phagocytosis effective, it was necessary to have specific antibody present in the plasma. Plasma without leukocytes was incapable of killing organisms. Tillett<sup>1</sup> has demonstrated that plasma obtained from patients with febrile diseases not due to a hemolytic streptococcus is bacteriostatic, as well as bactericidal, for certain strains of hemolytic streptococci. As a part of our studies on hemolytic streptococcal infections, it was desirable to determine the effect of adding sulfanilamide to whole blood and to plasma *in vitro* and to study its mode of action. We were especially interested in determining whether the bactericidal power of the blood could be enhanced, since we have shown previously that during the natural course of hemolytic streptococcal infections specific antibodies increased or appeared as a result of the infection.

### METHODS

To study the effect of sulfanilamide on the bactericidal action of whole blood, we used the method described by Spink and Keefer.<sup>2</sup> For the experiments samples of blood were obtained from various persons who were free from hemolytic streptococcal infections, because previous experience had taught us that the bactericidal action of whole blood from infected persons is frequently increased above that of control subjects, especially as the disease advances. The same strain of

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1 Tillett, W. S. The Bactericidal Action of Human Serum on Hemolytic Streptococci. I. Observations Made with Serum from Patients with Acute Infections and from Normal Individuals, *J. Exper. Med.* **65** 147, 1937, II Factors Which Influence the Phenomenon *in Vitro*, *ibid.* **65** 163, 1937.

2 Spink, W. W., and Keefer, C. S. Studies of Hemolytic Streptococcal Infection. II. The Serological Reactions of the Blood in Erysipelas, *J. Clin. Investigation* **15** 21, 1936.

the hemolytic streptococcus was used in all the tests reported. It was a group A strain that had been isolated from the circulating blood of a patient who died of puerperal sepsis. This strain was selected since it was found that few persons could kill small numbers of these organisms with their blood. The blood was studied for its streptococidal power with and without the addition of varying amounts of sulfanilamide. When variations from this technic were used it will be so stated.

#### EFFECT OF ADDING SULFANILAMIDE TO WHOLE BLOOD

To test the effect of sulfanilamide on the growth and the bactericidal power of the blood of various persons, the following plan was followed. A group A strain of the hemolytic streptococcus which had been recently isolated from the circulating blood of a patient with puerperal sepsis was tested against 30 samples of blood from patients without hemolytic streptococci or other infection. One-half a cubic centimeter of whole defibrinated blood was used with varying numbers

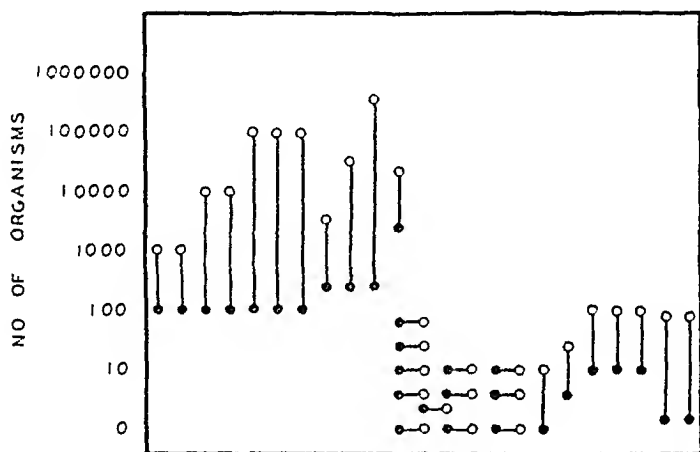


Chart 1—Bactericidal effect of sulfanilamide in whole blood. The solid dots represent the bactericidal power of 0.5 cc of whole blood without sulfanilamide, the circles with sulfanilamide, 10 mg per hundred cubic centimeters.

of organisms. When sulfanilamide was added to the blood, a freshly prepared 0.8 per cent solution was used so that the final concentration in the blood varied from 2.5 to 10 mg per hundred cubic centimeters. The number of organisms killed was determined from the number in the tube which failed to show any growth after twenty-four hours in a rotating machine in the incubator.

The first group of experiments was carried out with a concentration of sulfanilamide in the blood equal to 10 mg per hundred cubic centimeters. The results of the tests are recorded in chart 1. It is seen that the addition of sulfanilamide to whole blood was not in all cases followed by an increase in the bactericidal activity. Indeed, in many instances there was no difference between the bactericidal power of the blood with and that without sulfanilamide, but in no instance did sulfanilamide interfere with the bactericidal action of whole blood. In some cases, however, the number of organisms which were killed definitely increased after the addition of sulfanilamide, and the increase was more striking in the cases in which the blood alone contained bacterial antibodies. It is suggestive, at least, that in the presence of antibodies the addition of sulfanilamide may enhance the bactericidal power of the blood.

### EFFECT OF VARYING CONCENTRATIONS OF SULFANILAMIDE IN WHOLE BLOOD

From the foregoing experiments it seemed clear that in some samples of blood, with a concentration of 10 mg per hundred cubic centimeters, there was an increase in bactericidal power. We had to determine whether varying the concentration of sulfanilamide in these samples of blood would affect the number of organisms that were killed. The same sample of blood, with varying numbers of organisms and different concentrations of sulfanilamide per hundred cubic centimeters of blood, was studied. Two and one-half, 5, 7, 8 or 10 mg per hundred cubic centimeters was added to the blood. The results are shown in chart 2. In several cases the effect of higher concentrations, i e, 20, 30 or 40 mg per hundred cubic centimeters, was studied. It is shown in chart 2 that maximum effects were obtained when more than 5 mg per hundred cubic centimeters,

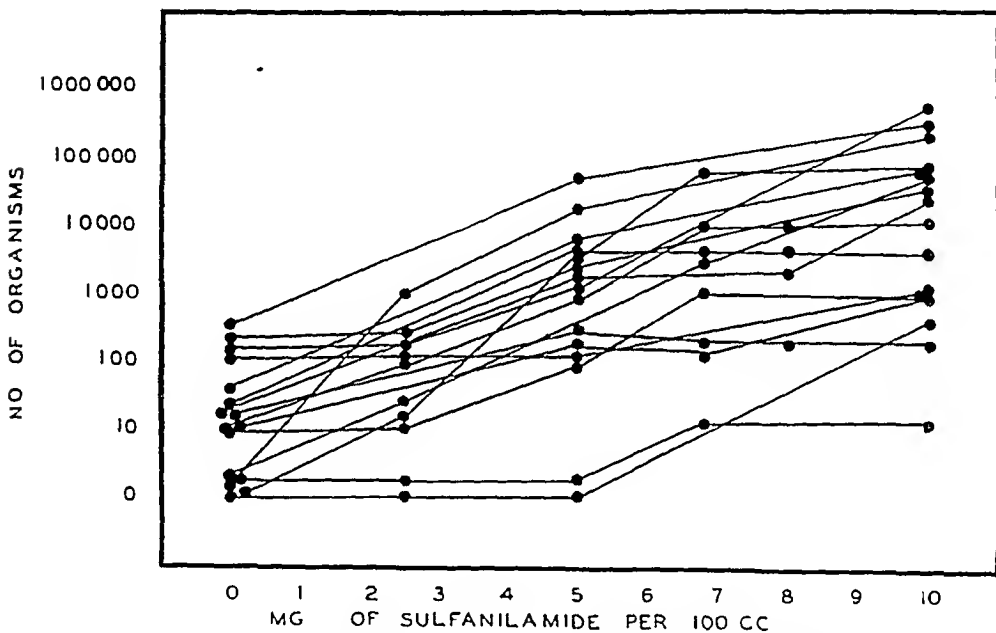


Chart 2—Bactericidal effect of varying amounts of sulfanilamide on different samples of blood showing bactericidal power

especially 7 mg or more, was added. We found no further enhancement of the action when amounts greater than 10 mg were added to the blood.

These observations indicate that in order to obtain a maximum effect on whole blood *in vitro* it is necessary to obtain a concentration in the blood of at least 5 mg per hundred cubic centimeters. The same effects on the bactericidal action of the blood could be demonstrated when the drug was administered by mouth provided the concentration reached 5 mg or more per hundred cubic centimeters of blood.

### EFFECTS ON THE WHOLE BLOOD OF ADMINISTERING SULFANILAMIDE BY MOUTH

To establish whether sulfanilamide when administered by mouth has the same effect on the blood as when added to it *in vitro*, 7 normal persons were given the drug by mouth so that the concentration in the blood varied from 4.6 to 6

mg per hundred cubic centimeters, then their blood was tested for bactericidal and bacteriostatic effects. These results are shown in table 1, and it can be seen that the effects were the same whether the drug was given by mouth or added to the blood in vitro, namely, bacteriostasis and bactericidal effects were observed.

#### EFFECT OF ADDING SULFANILAMIDE TO PLASMA

In previous studies, we were unable to show that blood plasma obtained from normal persons or from patients suffering from nonfebrile diseases is capable of killing various strains of hemolytic streptococci. This was true whether the plasma contained specific antibody or not. As a part of the present investigation,

TABLE 1—*Effect of Sulfanilamide on Whole Blood After Its Administration by Mouth*

Dilution of Culture	10 <sup>-1</sup>	10 <sup>-2</sup>	10 <sup>-3</sup>	10 <sup>-4</sup>	10 <sup>-5</sup>	10 <sup>-6</sup>	10 <sup>-7</sup>	10 <sup>-8</sup>
Whole blood	∞*	∞	∞	∞	0	0	0	1†
Whole blood plus sulfanilamide, 5.6 mg per 100 cc	∞	∞	3,000	0	0	0	0	
Whole blood	∞	∞	∞	∞	0	0	0	1
Whole blood plus sulfanilamide, 5.2 mg per 100 cc	∞	∞	∞	∞	20	0	0	
Whole blood	∞	∞	∞	∞	∞	0	0	4
Whole blood plus sulfanilamide, 4.6 mg per 100 cc	∞	1,000	10	0	0	0	0	
Whole blood	∞	∞	∞	∞	∞	∞	0	2
Whole blood plus sulfanilamide, 4.8 mg per 100 cc	∞	∞	∞	∞	∞	1,000	0	
Whole blood	∞	∞	∞	∞	0	0	0	2
Whole blood plus sulfanilamide, 6 mg per 100 cc	∞	∞	0	0	0	0	0	
Whole blood	—	—	∞	∞	∞	∞		2
Whole blood plus sulfanilamide, 5 mg per 100 cc	—	—	∞	∞	60	10		
Whole blood	∞	∞	∞	∞	∞	0	0	2
Whole blood plus sulfanilamide, 6 mg per 100 cc	∞	∞	260	0	0	0	0	

\* Innumerable colonies

† Total number of organisms in 10<sup>-8</sup> dilution

we studied the effect of adding sulfanilamide to plasma and compared the bactericidal action of whole blood and sulfanilamide with that of plasma and sulfanilamide. In all we studied 20 samples of plasma, with and without the addition of sulfanilamide, and in no case were we able to demonstrate a bactericidal effect with the strains employed. The results in 3 cases serve as examples, and they are shown in table 2. In each of the experiments 0.5 cc of whole blood or 0.5 cc of plasma was used. One tenth of a cubic centimeter of varying dilutions of organisms was added to each tube, and in the tubes containing sulfanilamide the total concentration of the chemical was equal to 10 mg per hundred cubic centimeters. The table shows that when whole blood was capable of destroying a certain number of organisms the same capacity could not be demonstrated for the plasma alone. Moreover, the addition of sulfanilamide did not change the capacity of plasma so far as destruction of organisms was concerned.

From these observations one concludes that leukocytes are necessary for the destruction of hemolytic streptococci *in vitro* even in the presence of sulfanilamide

We next turned our attention to the problem of bacteriostasis when organisms were added to plasma. After the addition of a measured number of organisms to blood plasma, the total number of organisms present at the end of two, four, eight, ten and twenty-four hours was determined in samples of plasma, with and without sulfanilamide. The results of an experiment which was typical are illustrated in chart 3. It was found that there were fewer organisms at the end of twenty-four hours in the sample of plasma containing sulfanilamide than in the sample without it. This indicates that there was some decrease in the rate of multiplication of organisms in the presence of sulfanilamide, but it was less striking than when whole blood was used.

TABLE 2—*Effect of Adding Sulfanilamide to Whole Blood and Plasma*

Dilution of Organisms	10 <sup>-1</sup>	10 <sup>-2</sup>	10 <sup>-3</sup>	10 <sup>-4</sup>	10 <sup>-5</sup>	10 <sup>-6</sup>	10 <sup>-7</sup>	10 <sup>-7</sup>
Patient 1								10*
Whole blood	+	+	0†	0	0	0	0	
Whole blood plus sulfanilamide	+	+	+	0	0	0	0	
Plasma	+	+	+	+	+	+	+	
Plasma plus sulfanilamide	+	+	+	+	+	+	+	
Patient 2								10
Whole blood	—	+	+	0	0	0	0	
Whole blood plus sulfanilamide	+	+	+	0	0	0	0	
Plasma	+	+	+	+	+	+	+	
Plasma plus sulfanilamide	+	+	+	+	+	+	+	
Patient 3								10
Whole blood	+	+	+	0	0	0	0	
Whole blood plus sulfanilamide	+	+	+	0	0	0	0	
Plasma	+	+	+	+	+	+	+	
Plasma plus sulfanilamide	+	+	+	+	+	+	+	

\* Total number of organisms in 10<sup>-7</sup> dilution

† + = growth after 24 hours

‡ 0 = no growth after 24 hours

These experiments with plasma *in vitro* seem to indicate that sulfanilamide reduces the rate of multiplication of hemolytic streptococci, but there is no evidence of a bactericidal effect. They also emphasize the importance of cells in destroying hemolytic streptococci *in vitro*.

#### STUDY OF THE BACTERIOSTATIC EFFECT OF SULFANILAMIDE

Since the bactericidal effect of sulfanilamide varied in different samples of whole blood, we had to determine whether or not the drug exerted a bacteriostatic effect in the samples in which it was not possible to show that the blood was sterilized. Two methods were used to study this problem. In the first, parallel series of tubes containing 0.5 cc of whole blood were seeded with varying numbers of organisms. One series of tubes contained sulfanilamide, the other did not. These tubes were sealed and placed in a rotating machine in the incubator for twenty-four hours. At the end of that time the tubes were opened, and the total number of organisms in them was determined by means of pour plates. Eighteen samples of blood were studied in this way, with the use of strain C, and the results are shown in chart 4.



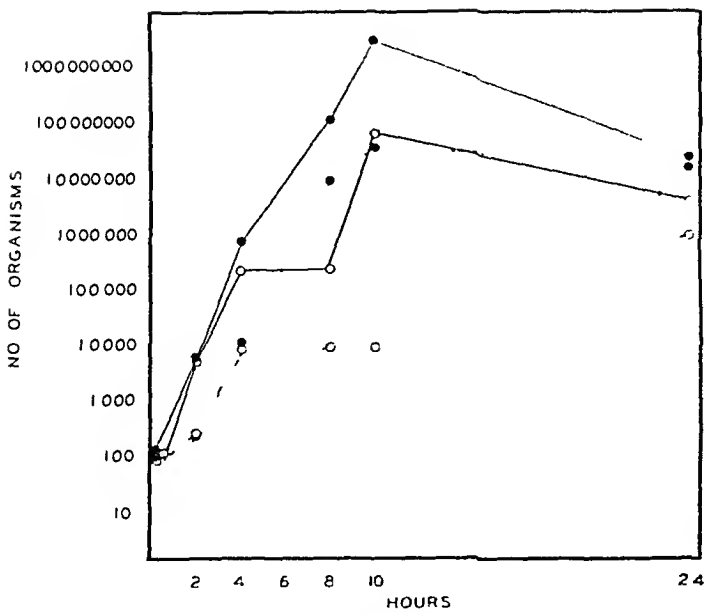


Chart 3—Comparison of the bacteriostatic effect of sulfanilamide in whole blood and in blood serum The broken line with solid dots represents blood, the solid line with solid dots, serum, the broken line with circles, blood with 10 mg of sulfanilamide per hundred cubic centimeters, and the solid line with circles serum with 10 mg of sulfanilamide per hundred cubic centimeters

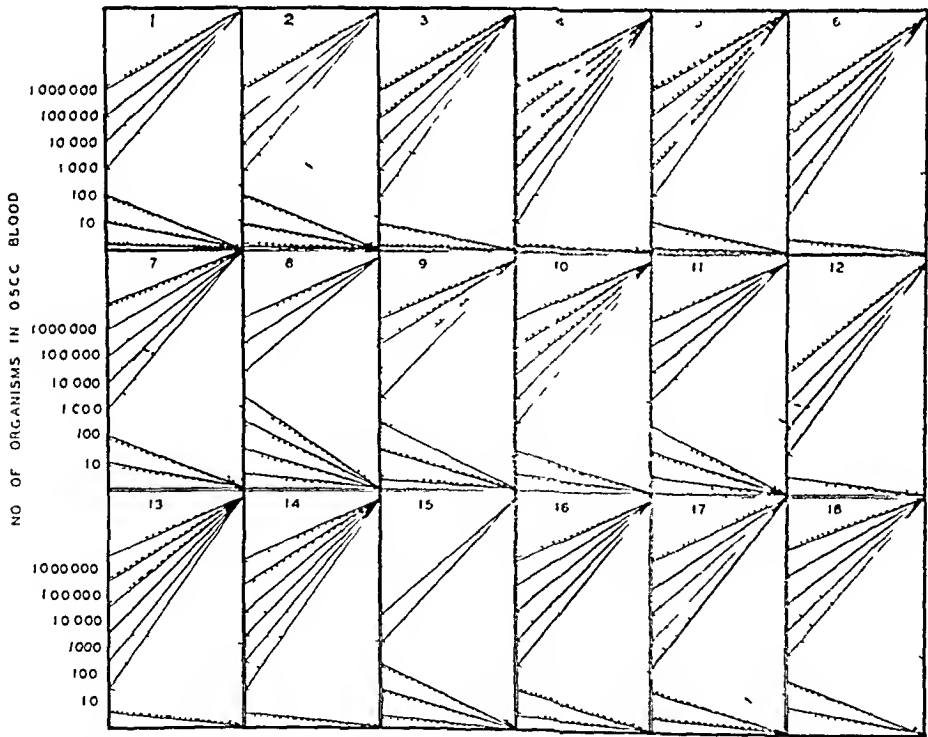


Chart 4—Bactericidal and bacteriostatic effect of sulfanilamide (10 mg per hundred cubic centimeters) in 18 different samples of whole blood with strain C The solid lines represent whole blood, the broken lines, whole blood and sulfanilamide The lines on the left of each square indicate the total number of organisms in 0.5 cc of blood The points on the right of each square indicate the total number at the end of twenty-four hours The point in the upper right hand corner of each square indicates infinity The point in the lowest corner of each square indicates no growth

The second method of studying bacteriostasis was to determine the growth at varying intervals after the inoculation of organisms into the blood. That is to say, the total number of organisms in the blood with and in that without sulfanilamide was determined two, four, eight, ten and twenty-four hours after incubation. The results are recorded in chart 5. In every case there was a decrease in the rate of reproduction of hemolytic streptococci when sulfanilamide was added to the blood, and in some instances the organisms failed to grow after twenty-four hours' incubation.

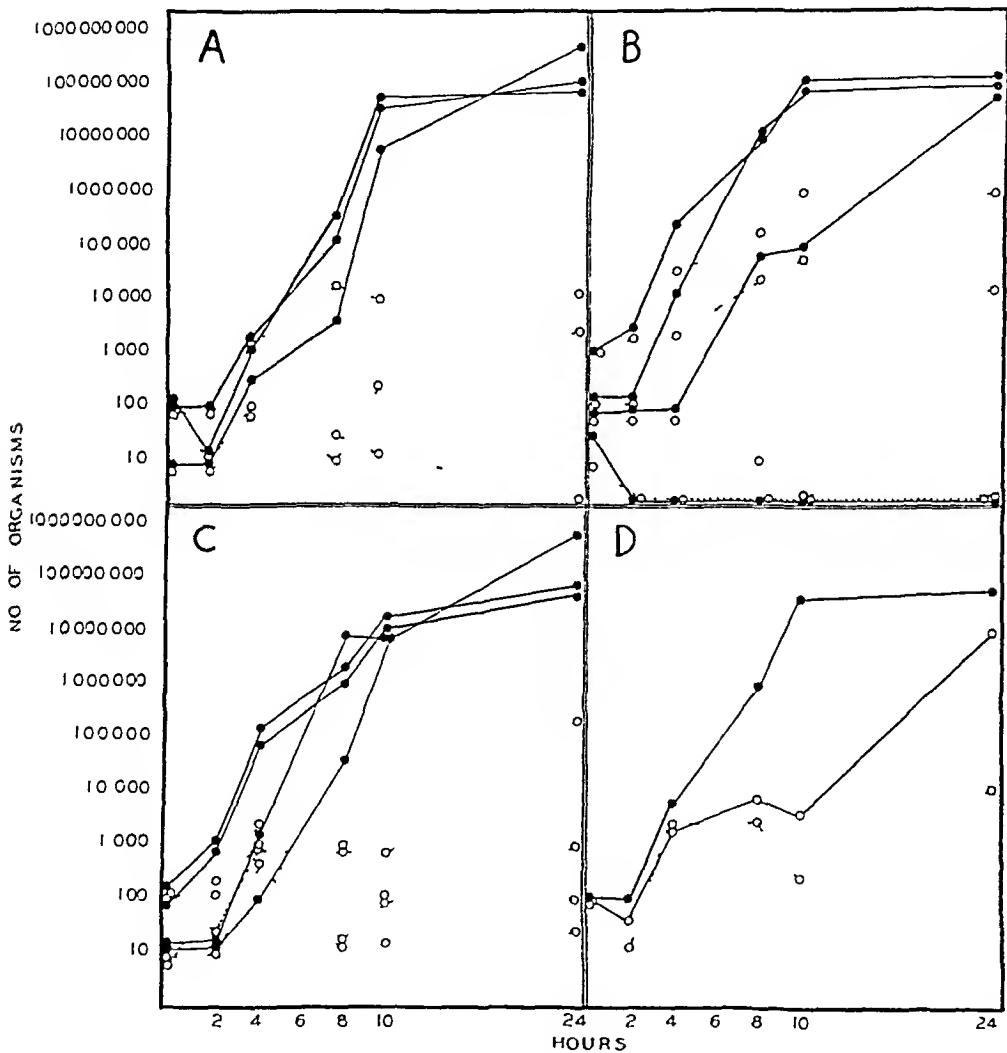


Chart 5—A, B and C, bacteriostatic effect of sulfanilamide (1 mg per hundred cubic centimeters) on whole blood with varying numbers of organisms in 3 subjects. The solid line represents blood, the broken line, blood with sulfanilamide. D, difference between the effects with 5 and with 10 mg per hundred cubic centimeters. The solid line with solid dots represents blood, the broken line, blood with 10 mg of sulfanilamide, and the solid line with circles, blood with 5 mg.

When the results of adding 5 and 10 mg per hundred cubic centimeters, respectively, were studied (chart 5), it was found that the inhibition of growth was somewhat greater with 10 than with 5 mg.

These experiments show that when sulfanilamide is added to whole blood *in vitro* so that the concentration is 10 mg per hundred cubic centimeters of blood there is bacteriostasis in every case. In some samples of blood it was possible to demonstrate a bactericidal effect that was greater when sulfanilamide was added than it was with the whole blood alone. This was more striking when the blood contained bactericidal properties without sulfanilamide and when small numbers of organisms were used.

In the instances in which there was an inhibition of growth, two phenomena were observed. 1. When small numbers of organisms were used there was often no evidence that multiplication took place, but the organisms were capable of reproduction when they were subcultured to mediums containing no sulfanilamide. 2. The inhibition was effective in increasing the lag phase, and the total number of organisms at the end of twenty-four hours was smaller in blood containing sulfanilamide than in whole blood without it.

#### COMMENT

The objective in the treatment of hemolytic streptococcal infections is to suppress the growth of organisms, prevent their spread from the point of invasion and, finally, destroy them completely. In the natural sequence of events this is accomplished by the summation of a number of factors, such as local inflammation, the presence of specific antibodies and active and viable phagocytes. There seems to be evidence available that sulfanilamide in the tissue fluids inhibits and reduces the growth and rate of multiplication of hemolytic streptococci provided the concentration is above 7 mg per hundred cubic centimeters. There is no evidence that this chemical destroys hemolytic streptococci through its direct action on the organism, nor is it clear that it stimulates either the accumulation of phagocytes or their activity. There is, however, suggestive evidence that in the presence of antibodies more organisms may be destroyed when sulfanilamide is present than when it is not. This may be due to a reduction in the substances which neutralize the antibodies present and those which are being elaborated. On this point more work is needed.

The destruction of hemolytic streptococci in the body is due to a complex process and, as stated, depends in large part on the cooperative activity of a number of factors. The general belief that these organisms are destroyed by intracellular ingestion is well supported by numerous observations in carefully controlled experiments. In the test tube at least, it can be shown that the destruction of hemolytic streptococci depends on the combined and cooperative action of specific antibody in the plasma and active viable phagocytes. There is good evidence that the

bacteria are sensitized by the antibody and in this way conditioned so that phagocytosis can take place. It is known also that without the presence of antibody the organisms grow freely and elaborate substances which destroy leukocytes (leukocidin) and red blood cells (hemolysin-streptolysin). There is additional evidence that during febrile diseases not due to hemolytic streptococcic infection there is a change in the properties of the blood plasma that inhibits the growth of some strains of organisms. This phenomenon has been studied especially by Tillett.<sup>1</sup> Its importance has not been studied sufficiently thoroughly in cases of human hemolytic streptococcic infection to be assessed relative to the defense mechanism of the body.

To explain the mode of action of sulfanilamide in hemolytic streptococcic infections, the following hypotheses have been proposed: 1. It stimulates phagocytosis. 2. It neutralizes toxins. 3. It acts by inhibiting the growth of organisms. 4. It actually is bactericidal under certain conditions. 5. It delays growth of organisms until mononuclear phagocytes accumulate. 6. The organisms are altered so that phagocytosis can take place.

These various hypotheses merit discussion.

One of the first questions studied was whether sulfanilamide has any effect on the bacteria themselves, that is to say, whether the drug acts on the bacteria and makes them more easily destroyed. Levaditi and Vaisman<sup>3</sup> maintained that streptococci grown in the animal body, and not in culture mediums, when injected into other mice are practically unaffected by prontosil therapy.<sup>4</sup> We have not been able to confirm this with the strains of hemolytic streptococci that we have used to infect mice, since organisms could be transferred from one mouse to another with identical results as far as the effect of sulfanilamide was concerned. Moreover, we found that organisms that were grown in mediums containing sulfanilamide for twenty-four or forty-eight hours were still as capable of producing fatal infections in mice with the same number as organisms that had not been exposed to the drug. In a word, we were not able to find that sulfanilamide changed the organism in such a way that when it began reproducing it failed to invade or produce a fatal infection in mice. Moreover, we were not able to find that such treatment enhanced the virulence of bacteria.

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3 Levaditi, C., and Vaisman, A. Action curative et préventive du chlorhydrate de 4'-sulfamido-2, 4-diamino-azobenzène dans l'infection streptococcique expérimentale, *Compt rend Acad d sc* **200** 1694, 1935, Action curative du chlorhydrate de 4'-sulfamido-2, 4-diaminoazobenzène et de quelques dérivés similaires, dans la streptococcie expérimentale, *Compt rend Soc de biol* **119** 946, 1935.

4 They used the original prontosil, the hydrochloride of 4-sulfamido-2',4'-diaminoazobenzene.

More recently, however, Meyer<sup>5</sup> has found that growing hemolytic streptococci in a serum medium containing a sulfanilamide-sugar compound causes clumping of the organism, decreases its virulence and inhibits production of toxin.

Lyons<sup>6</sup> reported that hemolytic streptococci which have been grown in serum containing sulfanilamide for fifteen or twenty subcultures are more vulnerable to phagocytosis and are killed in greater numbers by human blood after this procedure than before.

These studies are the first suggesting that the growth of hemolytic streptococci in vitro in the presence of sulfanilamide changes their virulence.

#### DOES SULFANILAMIDE AFFECT PHAGOCYTOSIS?

Bliss and Long<sup>7</sup> noted increased phagocytosis and a decrease in free cocci in the peritoneal cavities of mice infected with hemolytic streptococci and treated with sulfanilamide. It was not clear whether the decrease was due to stimulation of phagocytosis or to a change in the bacteria that rendered them more susceptible to phagocytosis. That phagocytosis is necessary for killing there is no doubt. The authors stated that the drug does not stimulate phagocytosis or protect the cells from the products of the bacteria. McKinney and Mellon<sup>8</sup> expressed the opinion that phagocytosis is conditioned by the previous bacteriostatic action of the drug. These observations receive indirect support from the studies of Ward and Lyons,<sup>9</sup> who showed that phagocytosis of rapidly growing, young, virulent hemolytic streptococci did not take place without the presence of specific antibody, whereas organisms in the noncapsulated phase or in old cultures were often phagocytosed without the presence of specific antibody. There is evidence, then, that sulfanilamide does not interfere with phagocytosis, although there is no evidence that it stimulates it. There is suggestive evidence that the bacteriostatic effect of sulfanilamide may enable phagocytes to take up more organisms and that in this way their destruction is accomplished.

5 Meyer, F. New Studies in Sulfanilamide Therapy, *Quart Bull Ser View Hosp* **3** 380 (July) 1938.

6 Lyons, C. The Effect of Sulfanilamide upon Human Virulent Hemolytic Streptococci, *Ann Surg* **108** 813 (Nov) 1938.

7 Bliss, E. A., and Long, P. H. Observations on the Mode of Action of Sulfanilamide, *J A M A* **109** 1524 (Nov 6) 1937.

8 McKinney, R. A., and Mellon, R. Sulfanilamide and Macrophage Response to Hemolytic Streptococcal Peritonitis in Mice, *Proc Soc Exper Biol & Med* **37** 333, 1937.

9 Ward, H. K., and Lyons, C. Studies on the Hemolytic Streptococcus of Human Origin. I. Observations on Virulent, Attenuated, and Avirulent Variants, *J Exper Med* **61** 515, 1935. Lyons, C., and Ward, H. K. II. Observations on the Protective Mechanism Against Virulent Variants, *ibid* **61** 531 1935.

Gay and Clark<sup>10</sup> concluded from their studies of experimental hemolytic streptococcic empyema in rabbits that the course of events in their animals treated with sulfanilamide was a bacteriostatic action of the drug, the outpouring of leukocytes and, finally, complete sterilization of the pleural cavity by the monocytes derived from the local tissues. They stated the belief that there is no evidence that the drug stimulates the localization of monocytes. From numerous experiments, they have found that the destruction of the hemolytic streptococci in the pleural cavity of the rabbit is the function of the monocytes but that it requires time for these cells to increase in large number. In the case of an infection due to organisms that are reproducing rapidly, invasion takes place before the infection can be localized and dealt with adequately by the monocytes. Thus its bacteriostatic action is an important function of sulfanilamide.

#### BACTERIOSTATIC AND BACTERICIDAL EFFECTS

In determining the bactericidal effect of any substance one must take into account that slight changes in culture mediums will often prevent growth of bacteria and that these effects are soon followed by the death of the organism. That is to say, when the environment is changed so that bacteria cannot multiply they often die, so that it is difficult and, indeed, of little value many times to differentiate bactericidal from bacteriostatic effects.

There seems to be general agreement among those who have studied the problem that sulfanilamide in concentrations of 1:10,000 causes a reduction in the growth of hemolytic streptococci in broth and even in the presence of blood serum. In the experience of Long and Bliss<sup>11</sup> this inhibition was effective only in increasing the lag phase of growth after two hours' incubation.

Colebrook, Buttle and O'Meara<sup>12</sup> demonstrated that whole blood or serum is both bacteriostatic and bactericidal when sulfanilamide is added to either *in vitro*. Moreover, the administration of sulfanilamide by mouth to man or monkeys is followed by a higher bacteriostatic and bactericidal action than that observed in normal blood or serum. These effects were observed only when small numbers of organisms were

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10 Gay, F. P., and Clark, A. R. On the Mode of Action of Sulfanilamide in Experimental Streptococcus Empyema, *J. Exper. Med.* **66** 535, 1937.

11 Long, P. H., and Bliss, E. A. Para-Amino-Benzene-Sulfonamide and Its Derivatives. Experimental and Clinical Observations on Their Use in the Treatment of Beta-Hemolytic Streptococcic Infection, Preliminary Report, *J. A. M. A.* **108** 32 (Jan 2) 1937.

12 Colebrook, L., Buttle, G. A. H., and O'Meara, R. A. Q. The Mode of Action of *p*-Aminobenzene Sulphonamide and Prontosil in Hemolytic Streptococcal Infections, *Lancet* **2** 1323, 1936.

used The same workers expressed the opinion that serum containing sulfanilamide kills almost as many organisms as whole blood, and they stated that probably the effect of the leukocytes is to enhance the killing of the cocci by the drug

The blood of rabbits, guinea pigs and mice is less effective in killing hemolytic streptococci than is human or monkey blood

Recent studies by Hoare<sup>13</sup> have shown that sulfanilamide has a bactericidal effect when it is added to normal human blood Our own studies show that sulfanilamide has always exerted a bacteriostatic effect when it is added to whole blood or plasma This was most striking when concentrations of 7 to 10 mg per hundred cubic centimeters were used together with small numbers of organisms We were unable to show that the addition of sulfanilamide to whole blood produced a bactericidal effect in all cases The variations in the effect were due in part to the presence or absence of antibodies in the samples of normal blood which were used in the tests, and we have recently found that there is considerable variation in the bactericidal effect of the drug when different specific serologic types of streptococci are used

#### NEUTRALIZATION OF TOXINS

Osgood and Brownlee<sup>14</sup> have expressed the opinion that the main action of sulfanilamide on the beta hemolytic streptococci is the neutralization of toxins They stated the belief that the drug does not kill these organisms directly, although the bactericidal properties of normal serum and, to some extent, phagocytosis of organisms by leukocytes are also operative In their opinion, there is no direct effect on phagocytosis The slowing of the rate of growth which has been observed by all investigators was attributed to the neutralization of toxins, and the bacteriostasis was interpreted to be probably incidental and not essential

The evidence for the neutralization of toxins was based on the observation that there was a decrease in the size of hemolyzed areas in blood agar plates about colonies exposed to sulfanilamide Unfortunately, the authors produced no evidence that filtrates from their cultures caused any destruction in their marrow cultures, either with or without sulfanilamide Recent work by Gross, Cooper and Lewis<sup>15</sup>

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13 Hoare, E D Bactericidal Changes Induced in Human Blood and Serum by Sulphamido-Chrysoidine and Sulphanilamide, *Lancet* **1** 655, 1938

14 Osgood, E E, and Brownlee, I E Culture of Human Marrow Studies on the Mode of Action of Sulfanilamide, *J A M A* **110** 349 (Jan 29) 1938

15 Gross, P, Cooper, F B, and Lewis, M Inhibition of Streptococcal Hemolysis by Sulfanilamide Compounds, *Proc Soc Exptl Biol & Med* **38** 275, 1938

has demonstrated that there was "a slight almost negligible inhibition of the hemolytic activity of streptococcic hemolysin by sulfanilamide" Huntington<sup>16</sup> has also found that the presence of sulfanilamide fails to prevent the production of fibrinolysin or erythrogenic toxin by the growing organism Osgood and Brownlee<sup>14</sup> suggested further that hemolytic streptococci would resemble a harmless saprophyte and be readily vulnerable to the ordinary defense mechanism of the body provided the toxins were neutralized, destroyed or prevented from forming by the presence of sulfanilamide We have found that even when there is no reproduction of the organism in vitro there may not be any destruction This observation suggests that some mechanism other than the neutralization or absence of toxin is necessary for the death of the organism in blood In the light of existing knowledge concerning the activity of hemolytic streptococci, it is difficult to believe that neutralizing toxin alone ever places them in the category of harmless saprophytes Indeed, Fothergill and Lium<sup>17</sup> have shown that antistreptococcus serum of high antitoxic value has no effect on the reproduction or the death of virulent streptococci in vitro We have found in unpublished experiments that addition of erythrogenic toxin to whole blood which was bactericidal caused no demonstrable decrease in the bactericidal properties of the blood

We can say, however, that we have noted bacteriostasis in tubes in which the organisms had survived but no hemolysis of the blood had taken place, which suggests at least that without reproduction there is no production of hemolysin

#### BACTERIOSTASIS IN MICE

From experiments with mice infected with mouse-virulent strains of hemolytic streptococci there seems to be evidence that the main action of the drug is that of bacteriostasis, since death is delayed only as long as the drug is injected<sup>11</sup>

To study further the effect of sulfanilamide, we observed its action in mice infected with hemolytic streptococci

*Experimental Studies*—We have found, in common with others, that the injection of sulfanilamide into mice which have been infected with a strain of hemolytic streptococcus that is mouse virulent will prevent death as long as the administration of the drug is continued When it is stopped many of the animals die Tables 3 and 4 show our results in the treatment of mice Table 3 indicates

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16 Huntington, R. W., Jr. Failure of Sulfanilamide to Prevent Hemolysis, Fibrinolysis, and Production of Erythrogenic Toxin by Hemolytic Streptococci in Vitro, *Proc Soc Exper Biol & Med* **38** 328, 1938

17 Fothergill, L. D., and Lium, R. Value of Commercial, Antibacterial Streptococcus Sera in Hemolytic Streptococcal Infections, *New England J Med* **211** 99, 1934



that the strain that we used killed mice with regularity when a  $10^{-1}$  dilution of a virulent strain was injected intraperitoneally and in a high percentage of instances when smaller numbers of organisms were injected

TABLE 3—*Summary of Results of Injecting Varying Numbers of Hemolytic Streptococci (Strain C-203) into Control Animals*

Dilution of 18 Hour Culture*	Number of Mice Infected	Number of Mice	
		Surviving	Dead
$10^{-2}$	3	0	3
$10^{-3}$	21	0	21
$10^{-4}$	18	0	45
$10^{-5}$	30	3	27
$10^{-6}$	5	2	3
$10^{-7} \dagger$	3	2	1
Total	110	7	103

\* Each mouse received 1 cc of culture dilution

†  $10^{-7}$  = 20 to 30 organisms per cubic centimeter

TABLE 4—*Summary of the Effect of Sulfanilamide on Hemolytic Streptococcic Peritonitis in Mice*

Number of Mice	Culture	Treatment Started After Infection	Total Amount of Drug, Mg		Days of Treatment	Number of Deaths																		Summary	
						Days																		Survived	Died
						1	2	3	4	5	6	7	8	11	12	16	17	21	22	30					
3	10 <sup>-2</sup>	—	0		3													0	3						
6	10 <sup>-2</sup>	4 hr	16	1	6													0	6						
6	10 <sup>-2</sup>	8 hr	8	1	6													0	6						
4	10 <sup>-3</sup>	—	0	0	4													0	4						
12	10 <sup>-3</sup>	Imme diately	125	7				1					6		2			3	9						
4	10 <sup>-3</sup>	4 hr	80		2			1	1									0	4						
4	10 <sup>-3</sup>	8 hr			4													0	4						
40	10 <sup>-4</sup>	—	0	0	40													0	40						
15	10 <sup>-4</sup>	Imme diately	125	7				1					2		2			5	10						
4	10 <sup>-4</sup>	4 hr	80	6														2	2						
4	10 <sup>-4</sup>	8 hr	72	6			1			1					2			2	2						
4	10 <sup>-4</sup>	12 hr	104	6	1								1		1			1	3						
3	10 <sup>-4</sup>	16 hr	80	6			1						1					1	2						
4	10 <sup>-4</sup>	20 hr	72	6				1					1		1			1	3						
10	10 <sup>-5</sup>	—	0	0	7	1	1	1										0	10						
12	10 <sup>-5</sup>	Imme diately	112	7				1					1		3		1	1	7						
9	10 <sup>-5</sup>	Imme diately	80	6									1		3			5	4						
6	10 <sup>-5</sup>	4 hr	32	1					1	1								3	3						
6	10 <sup>-5</sup>	8 hr	40	1					1				2					3	3						
3	10 <sup>-6</sup>	—	0	0				1	1	1								0	3						
3					1										2			0	3						

We next turned our attention to the study of the effect of injecting sulfanilamide into animals which had been infected with varying numbers of organisms. The treatment was begun immediately or five or eight hours after infection. The results are recorded in table 4.

When 1 cc of a  $10^{-3}$  dilution of a sixteen hour broth culture of the organisms was injected intraperitoneally into mice and treatment begun immediately by injecting 1 cc of an 0.8 per cent solution of sulfanilamide every six hours for four doses and then 1 cc every day, it was found that all the animals except 1 survived during the period of treatment. When the treatment was stopped, most of the animals died. When treatment was delayed four or eight hours, death occurred with regularity.

When dilutions of  $10^{-4}$  were used and treatment was started immediately or within four hours, most of the mice could be saved as long as treatment was continued. The same results were obtained when fewer organisms were used.

In brief, then, it can be said that sulfanilamide prevents the death of mice against 100 to 1,000 lethal doses of hemolytic streptococci as long as the use of the drug is continued. When it is stopped the fatality rate is high. This indicates that the drug is not bactericidal for the organisms in the mouse but delays their growth so that death does not occur as long as it is administered. It is possible, of course, that the reason these organisms grow so freely once the drug is discontinued is the lack of specific antibodies in these animals. That is to say, mice are unable to produce antibacterial antibodies, and since the effect of the drug is no longer operative, the infection progresses and kills the animal.

#### COMMENT

In summing up, then, it can be said that sulfanilamide has a definite effect on the growth of hemolytic streptococci in vitro and in vivo. This is suggested by inhibitory and even bactericidal effects. While these effects are only slight in some cases, nevertheless they are probably of great importance for the final destruction of the bacteria by the defense mechanisms of the body. These conclusions are supported by in vitro as well as in vivo experiments.

From the experimental as well as the clinical evidence so far we are forced to conclude that at least two conditions are essential for the optimum therapeutic action of sulfanilamide. The chemical must be present in sufficient concentration to produce optimum bacteriostasis, and the body's defense mechanism must acquire or retain the power to destroy viable organisms. From our own experiments there is evidence that a concentration of at least 7 to 10 mg per hundred cubic centimeters is necessary for maximal bacteriostasis and that specific antibody and active phagocytosis are necessary for destruction. In experimental animals mice and rabbits, the body is rid of organisms by means of phagocytosis, and the role of specific antibody is less certain.

It is perhaps not wholly justifiable to explain what happens in man on a basis of results in vitro and in animal experiments. It has been

pointed out by Holman and Duff<sup>18</sup> that in experimental studies the most virulent strains of bacteria are used and the most sensitive animals are chosen. There is no such preliminary contact between organism and tissues as is present in the stage of invasion, and defenses must, of necessity, be mobilized rapidly if they are to be effective. The same authors said that there is good evidence that sulfanilamide is most effective in the progressive stages of an infection in which active and continuous tissue reactions are taking place and that the bacteriostatic effect of the drug often tips the balance in favor of a cure.

In other words, there are good reasons for believing that recovery from a hemolytic streptococcal infection depends on the mobilization of the body's defenses so that the effects of the bacteria can be neutralized. Once the defense mechanism gains the upper hand, a definite cure takes place. If, on the other hand, the bacteria multiply rapidly, injure tissues, invade the body with rapidity and overwhelm it before the defenses can be mobilized or increased, then the balance will be tipped the other way. For the present, at least, it seems safe to say that sulfanilamide slows the growth of the organisms and in this way allows the defense mechanism of the tissue to mobilize in an effective manner.

There are many problems to be studied and worked out, especially the action of sulfanilamide on the defensive mechanisms of the body. Until such information is available it is well not to draw any rigid conclusions concerning the full mechanism by which this drug exerts its effects.

#### SUMMARY AND CONCLUSIONS

From a study of the mode of action of sulfanilamide *in vitro* and *in vivo*, the following facts emerged:

- 1 When sulfanilamide was added to whole defibrinated blood so that the concentration was 7 mg or more per hundred cubic centimeters, there was definite bacteriostasis, and in some instances a definite bactericidal effect was demonstrated.

- 2 We were unable to demonstrate a bactericidal effect of sulfanilamide when it was added to plasma, although bacteriostasis was present in plasma containing sulfanilamide. This bacteriostasis was less striking in plasma than it was in whole blood.

- 3 The samples of blood which showed a bactericidal effect with sulfanilamide were those containing some natural antibodies. It is suggested, therefore, that sulfanilamide may enhance the bactericidal effect of whole blood provided natural antibodies are present.

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<sup>18</sup> Holman, W. L., and Duff, G. L. Sulphanilamide and Similar Compounds in Chemotherapy, *Am J M Sc* **195** 378, 1938.

4 In the cases in which it was not possible to demonstrate a bactericidal effect, a bacteriostatic effect was shown. When the number of organisms was small there was almost complete bacteriostasis, when the inoculum was larger the rate of multiplication was slower, and the number of organisms at the end of twenty-four hours was less than in the controls.

5 It appears that antibodies are important in destroying hemolytic streptococci in vitro even in the presence of sulfanilamide.

6 The principal action of sulfanilamide in vitro is to slow the growth of the organism. It has no direct bactericidal effect on any serologic type of hemolytic streptococci.

Miss Marjorie L. Jewell and Miss Eleanor M. Fleming rendered technical assistance.

# COMPARATIVE EFFECTS ON EARLY SYPHILIS OF COMBINED AND OF ALTERNATING TREATMENT

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Continuous treatment is generally acknowledged to be superior to the intermittent type in the treatment of early syphilis. The simplest and most commonly used form of continuous therapy consists of courses of an arsphenamine alternating with courses of a heavy metal. Various forms of combined treatment, in which the two types of drugs have been given at the same time through at least part of the treatment, also have been widely used. In most of these modifications, the period of simultaneous administration has been comparatively short, or treatment was given intermittently rather than continuously. Stokes<sup>1</sup> more recently has used a "simultaneous (concurrent) continuous" form of therapy in which the individual courses are much longer than the intervals between courses. The results of this particular form of treatment have not been reported as yet.

In the last ten years in the syphilis clinic of the Stanford University School of Medicine, two plans of treatment have been used for early syphilis. Formerly, treatment was carried out with alternating courses of neoarsphenamine and iodobismutol<sup>2</sup> but more recently a system of combined therapy resembling the simultaneous method described by Stokes has been used. The purpose of this paper is to compare the clinical and serologic results obtained by these two methods of therapy.

In the alternating type of treatment, courses of ten weekly injections of neoarsphenamine were alternated with courses of twenty weekly injections of iodobismutol, except for the fact that for the first ten weeks the two drugs were given simultaneously. The usual dose of

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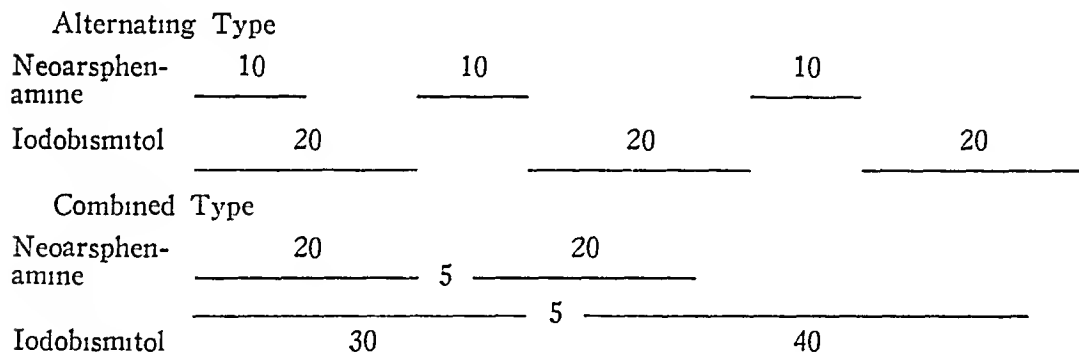
1 Stokes, J. H. *Modern Clinical Syphilology: Diagnosis, Treatment, Case Studies*, Philadelphia, W. B. Saunders Company, 1934, p. 767.

2 The term iodobismutol as used in this report refers to iodobismutol and to iodobismutol with saligenin. The former was used in the majority of the cases, but in the last two years of the study only the latter was available.

neoarsphenamine was 0.6 Gm for men and 0.45 Gm for women. The dose of iodobismutol was 2 cc. In a few cases one or more courses of maphaisen were substituted for courses of neoarsphenamine, and occasionally the initial course of neoarsphenamine was given without iodobismutol. In some cases sobisminol was used in place of iodobismutol, there were others in which the patients were given a course of mercuric salicylate late in the course of treatment, but never before at least two courses of bismuth had been administered.

In the combined type of treatment, neoarsphenamine and iodobismutol were given simultaneously once every week for a twenty week period. Neoarsphenamine was then omitted for five weeks, after which a second course of twenty injections was given. The initial course of iodobismutol was continued until it equaled thirty doses, and a second course, of forty doses, was given after an interval of five weeks. The usual dose of neoarsphenamine was 0.45 Gm for both men and women, and the dose of iodobismutol was 2 cc. The variations in the drugs which were used were similar to those on the alternating type except that in no instance was mercury included.

A diagram of the two types of treatment follows. The lines indicate courses of weekly injections, and the figures, the number of weeks of treatment.



The material studied consisted of 236 cases of primary or secondary syphilis in which the alternating type of treatment was given and of 81 similar cases in which the patients received the combined type. No patients were included who had not received at least twenty injections within a period of not less than five months.

There are a number of ways by which the effectiveness of the treatment of early syphilis may be evaluated. The most important of these are the serologic response, the incidence of involvement of the nervous system and the incidence of serologic or clinical relapse. We have appraised our results on the basis of these criteria.

The serologic results obtained by the two types of treatment at the end of five and of eighteen months are compared in table 1.

Of the patients whose treatment was started in the seronegative primary stage, all but 1 continued to present a seronegative reaction. No significance can be attached to a single relapse. Of the patients whose condition was initially seropositive, a higher percentage of reversals in the Wassermann reaction was observed at five months among those receiving the combined type of treatment. The same difference, although less marked, was observed at eighteen months.

An examination of the cerebrospinal fluid was carried out at some time after the first six months of treatment for every patient who did

TABLE 1—*Serologic Results Five Months and Eighteen Months After the Beginning of the Alternating and of the Combined Type of Treatment*

	Type of Treatment	
	Alternating	Combined
<b>Seronegative primary syphilis</b>		
Total number of patients	34	14
Seronegative reactions at 5 mo	31	14
Patients examined serologically at 18 mo	20	5
Seronegative reactions at 18 mo	20	4
<b>Seropositive primary and secondary syphilis</b>		
Total number of patients	202	67
Patients examined serologically at 5 mo	150	55
Seronegative reactions at 5 mo	111 (62%)	46 (79%)
Seropositive reactions at 5 mo	69 (38%)	12 (21%)
Patients examined serologically at 18 mo	114	25
Seronegative reactions at 18 mo	16 (84%)	23 (92%)
Seropositive reactions at 18 mo	18 (16%)	2 (8%)

TABLE 2—*Incidence of Positive Serologic Reactions of the Cerebrospinal Fluid with the Alternating and with the Combined Type of Treatment*

	Type of Treatment	
	Alternating	Combined
No. of cerebrospinal fluids examined	150	43
No. with positive reactions	24	7
Percentage of positive reactions	16%	16%

not refuse to undergo spinal puncture. The results, given in table 2, show the same incidence of involvement of the nervous system with the two types of treatment.

Although the incidence of involvement of the nervous system is not affected by the type of treatment, the combined form shows a slight advantage over the alternating in effecting serologic reversal. This is of minor importance, since the final criterion of therapeutic efficiency is the clinical outcome, which is not dependent on reversal of the Wassermann reaction. A much more valuable indication of the effectiveness of therapy is the frequency of clinical or serologic relapse. The incidence of relapse observed with the two types of treatment in our series

is shown in table 3. The relapses have been divided into two types, those in which only the serologic reactions became positive and clinical relapses. All the clinical relapses were of the mucocutaneous type, and all were accompanied by recurrence of the positive Wassermann reaction.

This table indicates that the combined type of treatment is inferior to the alternating type in the prevention of relapse, but the significance of this difference is modified by the consideration of several factors. The most important of these are the regularity of treatment, the amounts of antisypilitic drugs given and the total period of observation.

Therapy was considered to be regular when more than 80 per cent of the appointments for treatment were kept and irregular when the attendance was less than 80 per cent. This measure of regularity does

TABLE 3—*Incidence of Relapse with the Alternating and with the Combined Types of Treatment*

	Type of Treatment	
	Alternating	Combined
Total number of cases	236	81
Total number of relapses	18 (7.6%)	10 (12.3%)
Number of serologic relapses	15 (6.3%)	6 (7.4%)
Number of mucocutaneous relapses	3 (1.3%)	4 (4.9%)

TABLE 4—*Incidence of Relapse in Relation to the Regularity of Treatment*

	Type of Treatment	
	Alternating	Combined
Relapses with regular treatment	6	8
Relapses with irregular treatment	12	2

not distinguish prolonged irregular treatment from more or less regular treatment interspersed with periods of complete lapse. The incidence of relapse in relation to the regularity of treatment with the two types of therapy is shown in table 4.

Since the majority of relapses with the alternating type of therapy occurred in the patients receiving irregular treatment, it seems that this irregularity must have contributed to their production. On the other hand, most of the relapses with the combined type occurred in patients receiving regular treatment, indicating that the type of treatment itself was probably at fault. This difference is of even greater significance than is indicated in the table because the average regularity of attendance of all patients in the group with alternating treatment was greater than that in the group with combined treatment, being 88 per cent and 83 per cent, respectively.



In table 5 the total amount and the number of doses of neoarsphenamine and of iodobismutol given in the alternating and of those given in the combined type of therapy are shown. In the few cases in which mapharsen or sobisminol was substituted for a part of the treatment, a conversion was made to equivalent doses of neoarsphenamine and iodobismutol in preparing the table.

The patients who received the alternating type of therapy were given slightly more bismuth but considerably less neoarsphenamine than those who received the combined type. This occurred in spite of the fact that the average duration of therapy was only sixteen months for the combined type, as compared with nineteen months for the alternating type.

In the treatment of early syphilis, the drug of primary importance is generally considered to be arsphenamine or one of its derivatives. One

TABLE 5—*Total Amounts and Number of Doses of Neoarsphenamine and of Iodobismutol Given in the Alternating and in the Combined Type of Treatment*

	Type of Treatment	
	Alternating	Combined
Neoarsphenamine		
Average number of doses	29	37
Average total dose in Gm	15	18
Iodobismutol		
Average number of doses	49	45
Average total dose in Gm	5.8	5.5

would therefore expect that patients receiving larger amounts of these preparations would show better clinical results. This expectation is not fulfilled in our series, since the group given combined therapy, which showed a higher incidence of relapse than that given alternating therapy, received a larger average total amount of neoarsphenamine. The slight difference between the amount of bismuth given and the average duration of therapy in the two groups is too small to be of much significance and is probably explained by the fact that a number of patients in the series receiving combined therapy were still under treatment at the time this study was made.

The most important difference between the two groups, aside from the method of treatment, is in the average total period of observation, which was twenty-eight months for the series receiving alternating therapy and only eighteen months for that receiving combined therapy. The average time of relapse in the group given alternating therapy was twenty-three months after the beginning of treatment. Since the group given combined therapy was observed for only eighteen months, additional relapses would be expected to occur. In fact, several such

relapses have been observed since this study was terminated. It is therefore of particular significance that the group given combined treatment showed a higher incidence of relapses in spite of a much shorter period of observation.

Since the inferior results of the combined type of therapy appear more obvious when regularity of treatment, total dosage of drugs and duration of observation are considered, another explanation for this difference in therapeutic effect must be sought. Experimental evidence reported by various observers<sup>3</sup> indicates that prolonged use of any therapeutic agent, particularly in small doses, may lead to drug fastness. This evidence suggests that the long courses, separated by only short intervals, used in the combined type of treatment may be the cause of its inferiority.

#### SUMMARY AND CONCLUSIONS

1 The results of treatment in a series of 81 patients with early syphilis given combined neoarsphenamine and bismuth therapy are compared with the results in a similar series of 236 patients receiving an alternating type of treatment.

2 The frequency of serologic reversal at the end of five and of eighteen months of treatment was slightly greater for the patients given combined treatment than for those given the alternating type. This fact is of minor importance, since the rate of serologic reversal is not a satisfactory index of therapeutic efficiency.

3 The incidence of abnormal cerebrospinal fluids was the same in the two series.

4 The incidence of relapse, both clinical and serologic, was greater among the patients given combined treatment than among those given the alternating type. When the factors of regularity of treatment, total dosage of the drugs and duration of observation are taken into consideration, this difference assumes an added significance. Since the prevention of relapse is the most important indication of efficiency of treatment, the inferiority of the combined type of therapy in this respect is sufficient to make further use of this type of treatment undesirable.

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3 Akatsu, S., and Noguchi, H. The Drug Fastness of Spirochetes to Arsenic, Mercurial and Iodide Compounds in Vitro, *J. Exper. Med.* **25** 349, 1917. Brown, W., and Pearce, L., cited by Stokes<sup>1</sup>. Feldt, A. Ueber Arzneifestigung von Spirochäten im Tierversuche, *Klin. Wchnschr.* **11**:1378, 1932. Krantz, W. Untersuchungen über die Wirkungen ungenügender Salvarsanmengen bei experimenteller Kaninchensyphilis, *München med. Wchnschr.* **80** 2040, 1933.

# Progress in Internal Medicine

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## DISEASES OF THE HEART

A REVIEW OF SIGNIFICANT CONTRIBUTIONS MADE DURING 1938

ASHTON GRAYBIEL, M D

WITH THE EDITORIAL ASSISTANCE OF

PAUL D WHITE, M D

BOSTON

All students of heart disease will welcome the appearance of the *British Heart Journal*, which is being published at the request of the Cardiac Society of Great Britain and Ireland. There, it will fill a need which has been long felt and hitherto neglected. Being addressed chiefly to practicing physicians and cardiologists, it must not be regarded as merely a successor to *Heart*, which was restricted in scope. This journal will soon command a leading position in the field if it follows the precept expressed by Sir Thomas Lewis in the foreword as follows:

The success of the new journal will depend upon the quality and not primarily upon the quantity of the matter which it publishes. Originality of observation and of view will be the touchstone of quality. The work of editing is uncreative; an editor can publish only what is offered, he will use most of what is offered. The journal's success is governed, therefore, from the source of the material. The best contributors will submit for publication only sound and original matter and thought. They will edit their own work, will judge their own text impartially and will prune it ruthlessly, thinking of the standard of work accomplished and to be reported and not of personal interest; they will prepare their manuscript in all particulars to save further labour; they will facilitate the reading by every device of conciseness, of simplicity, of clarity, and of accuracy, in composing text, figure explanation, and reference, for every hour so spent by one who writes will save countless hours by the many who afterward read. They will remember that the work of editing is a gratuitous and unenviable task, and they will bow loyally to editorial decision.

### ELECTROCARDIOGRAPHY

Asher and Hoecker<sup>1</sup> have described a device which, when attached to an electrocardiograph, permits immediate and continuous viewing of the electrocardiogram. This device consists essentially of a moving

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From the Cardiac Clinic of the Massachusetts General Hospital

1 Asher, G., and Hoecker, F. The Lag-Screen Belt Electrocardiogram, *Am Heart J* **16** 51, 1938

endless belt coated with material which phosphoresces when exposed to the light beam of the electrocardiograph. The degree of phosphorescence is sufficient to define the wave form so that it appears much as it does in the electrocardiogram (only the finest details are lost), thus permitting adequate inspection of the complexes of a considerable strip of successive beats. The many advantages of this apparatus for clinical and teaching use are readily apparent.

Wilson and Johnston<sup>2</sup> have reviewed the history of the development of the vectorcardiogram and have described their own recording apparatus. A vector is a line, or a quantity that may be represented by a line, conceived to have both a fixed length and a direction in space but no fixed position. Consequently, since the resultant electromotive force produced by the heart at a given instant has both magnitude and direction, it may be represented by a vector drawn with the center of Einthoven's triangle as its origin. When the excitatory process in the heart is advancing or retreating, the size and direction of this vector vary from instant to instant so that its terminus describes a continuous curve. The relations between the vectorcardiogram and the three leads of the standard electrocardiogram have been clearly described by the authors and many examples of different types of curves shown. Conclusions as to the ultimate usefulness of the vectorcardiogram have been avoided, but some of its possibilities have been pointed out.

Sigler<sup>3</sup> has observed definite changes in the appearance of the QRS and T waves in the electrocardiogram following alterations from the recumbent to the sitting or standing position. The change may occur in the T wave alone, the amplitude diminishing or T becoming inverted in lead III or in leads II and III. The changes in the QRS complex consist chiefly in shifts of the electrical axis. The author has discussed certain theoretic implications and has concluded that the changes observed do not conform to the theory of the Einthoven equilateral triangle, because the shift in the electrical axis is not always the same as that predicted from the supposed shift of the anatomic axis. The preferred explanation is that on alteration of body posture there occurs a change in contact of the adjacent conducting mediums with different portions of the heart, thereby producing variations in conduction. As the author has stated, it is truly important to know the posture of the subject when the tracing was taken before attaching pathologic significance to certain apparent abnormalities.

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2 Wilson, F. N., and Johnston, F. D. The Vectorcardiogram, *Am Heart J* **16** 14, 1938.

3 Sigler, L. H. Electrocardiographic Changes Occurring with Alterations of Posture from Recumbent to Standing Positions, *Am Heart J* **15** 146, 1938.

Several authors<sup>4</sup> have described the electrocardiographic findings following the administration of various drugs and following nerve stimulation. Of particular interest is the report by Chamberlain, who found that resection of the cervical sympathetic ganglions has no effect on the form of the electrocardiogram. He also found that stimulation of the left sympathetic ganglion produces no constant changes but that stimulation of the one on the right may decrease the amplitude of R or increase T or both. The changes lasted only for a few minutes after the stimulation ceased.

Hill,<sup>5</sup> while trying various chest leads, found that whenever three leads were taken in the usual order from any three points, the sum of the first and third was always equal to the second. He then charted the potential distribution on the surface of the chest throughout the cardiac cycle, which suggested that the current to which the electrocardiogram is due runs around the thoracic wall and not through the chest, as hitherto commonly assumed. This is simply another piece of evidence which, when added to the rest, seems to indicate that the theory of the equilateral triangle and the meaning of the term axis deviation will need modification.

#### ROENTGENOLOGY

Robb and Steinberg<sup>6</sup> have described a practicable procedure which has enabled them successfully to visualize the chambers of the heart

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4 Chamberlain, E. N. The Results of Sympathetic Stimulation and Extirpation on the Human Electrocardiogram, *Clin Sc* **3** 267, 1938. Winkler, A. W., Hoff, H. E., and Smith, P. K. Electrocardiographic Changes and Concentration of Potassium in Serum Following Intravenous Injection of Potassium Chloride, *Am J Physiol* **124** 478, 1938. Volpitta, P. P., and Marangoni, B. A. Electrocardiographic Studies During Anesthesia with Intravenous Barbiturates, *J Lab & Clin Med* **23** 575, 1938. Dameshek, W., Loman, J., and Myerson, A. Human Autonomic Pharmacology. VII. The Effect on the Normal Cardiovascular System of Acetyl-Beta-Methylcholine Chloride, Atropine, Prostigmin, Benzedrine, with Especial Reference to the Electrocardiogram, *Am J M Sc* **195** 88, 1938. Stewart, H. J., and Watson, R. F. The Effect of Digitalis on the Form of the Human Electrocardiogram, with Special Reference to Changes Occurring in the Chest Lead, *Am Heart J* **15** 604, 1938. Hafkesbrang, R., and MacCalmont, W. The Effect of Sodium Amytal, Sodium Barbitol and Nembutal on the Electrocardiogram, *J Pharmacol & Exper Therap* **64** 43, 1938. Miller, J. R., and Van Dellen, T. R. Electrocardiographic Changes Following the Intravenous Administration of Magnesium Sulfate, *J Lab & Clin Med* **23** 914, 1938. Stearns, W. H., Drinker, C. K., and Shaughnessy, T. J. Electrocardiographic Changes Found in Twenty-Two Cases of Carbon Monoxide (Illuminating Gas) Poisoning, *Am Heart J* **15** 434, 1938.

5 Hill, A. Analysis of the Normal QRS Deflection, *Lancet* **2** 1110, 1938.

6 Robb, G. P., and Steinberg, I. Practical Method of Visualization of Chambers of the Heart, the Pulmonary Circulation, and the Great Blood Vessels in Man, *J Clin Investigation* **17** 507, 1938. Visualization of the Chambers of the Heart, the Pulmonary Circulation and the Great Blood Vessels in Man. A Practical Method, *Am J Roentgenol* **41** 1, 1939.

and the great vessels in the thorax. The method consists of the rapid injection of 25 to 45 cc of a 70 per cent solution of diodrast into a vein in the arm and the obtaining of roentgenograms when the chambers of the heart and the blood vessels are filled with the material that is opaque to the roentgen ray. Diodrast was found to have usually only mild pharmacologic effects when injected, only occasionally were severe reactions observed. This method will aid in the recognition of abnormalities of the mediastinal and hilar blood vessels and in the differentiation of these vessels from adjacent structures, such as mediastinal neoplasms. Visualization of the cardiac chambers, the ventricular walls, the interventricular septum and the valves will provide information about the normal and the diseased heart heretofore unobtainable. The authors have emphasized the fact that the method promises to be of practical value in the differential diagnosis of heart disease.

#### CARDIAC ARRHYTHMIAS

Stewart and his co-workers<sup>7</sup> made observations on the effect of abnormal rhythms on the circulation. They found that auricular fibrillation, auricular flutter, paroxysmal auricular and paroxysmal ventricular tachycardia in patients without congestive failure are associated with decrease in the cardiac output per minute and per beat, decrease in velocity of blood flow, dilatation of the heart and decrease in the work of the heart per beat. As a consequence these patients fall in the heart failure zone when the abnormal rhythm is present. On the other hand, in instances of heart block, sinus bradycardia and coupled rhythm, although the cardiac output per minute is decreased, the output per beat is increased, and the work per beat is commensurate with the size of the heart. Thus, the rapid abnormal cardiac rhythms are associated with marked decrease in the functional capacity of the heart, while the slow abnormal rhythms are not incompatible with a normal circulatory function when the subject is at rest.

*Abnormally Short PR Interval*—Clerc and his associates<sup>8</sup> have described instances of shortening of the PR interval in the electrocardiogram which was not associated with anomalies of the QRS complex. This stands in contrast to the short PR interval associated with

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7 Stewart, H. J., Detrick, J. E., Crane, N. F., and Thompson, W. P. Studies of the Circulation in the Presence of Abnormal Cardiac Rhythms. Observations Relating to Rhythms Associated with Rapid Ventricular Rate and to Rhythms Associated with Slow Ventricular Rate, *J. Clin. Investigation* **17** 449, 1938.

8 Clerc, A., Levy, R. and Cristesco, C. A propos du raccourcissement permanent de l'espace P-R de l'électrocardiogramme sans déformation du complexe ventriculaire, *Arch. d. mal. du cœur* **31** 569, 1938.

prolongation of QRS, which has been recognized for years. Certain clinical affinities exist between the two types, namely, their appearance in young persons with irritable but otherwise normal hearts and the benignity of the prognosis.

*Bundle Branch Block*—Yater<sup>9</sup> has written a comprehensive and critical treatise on the pathogenesis of bundle branch block. The important literature on this subject has been reviewed, including anatomic, physiologic, histopathologic and clinical studies. Especial emphasis has been given to his own pathologic studies in 16 cases and to 6 cases studied by means of serial sections through the conduction system. He found that bundle branch block is due usually to coronary atherosclerosis and less commonly to rheumatic involvement or to hypertension resulting in strain of the left ventricle and impairment of the nutrition of the endocardium and bundle branch. His studies showed that bundle branch block is usually associated with bilateral bundle branch lesions, although one branch is usually more seriously affected than the other and probably determines the essential form of the curve. The adjective right or left when applied to bundle branch block merely indicates the branch more seriously affected. He concluded that any increase of the QRS interval beyond 0.1 second may indicate lesions of the bundle branches and that a bundle branch need not be entirely destroyed at any level in order to produce the characteristic electrocardiographic changes.

*Paroxysmal Bundle Branch Block*—Comeau, Hamilton and White<sup>10</sup> have presented in detail 13 cases of paroxysmal bundle branch block and have added to their analysis 58 cases previously reported. They have pointed out that this arrhythmia is associated with serious organic heart disease and should be sharply differentiated from bundle branch block with a short PR interval, which is of no serious significance. Paroxysmal bundle branch block (without a very short PR interval) is most often due to coronary sclerosis but in some instances is associated with rheumatic heart disease, diphtheria and factors that cannot clinically be ascertained. Although physiologic changes may act as precipitating factors, they are effective only in the presence of actual changes in the conducting tissue. The authors believe that the prognosis is similar to that in permanent bundle branch block and depends upon the type and severity of the associated heart disease.

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9 Yater, W. M. Pathogenesis of Bundle Branch Block. Review of the Literature, Report of Sixteen Cases with Necropsy and of Six Cases with Detailed Histologic Study of the Conduction System, *Arch Int Med* **62**:1 (July) 1938.

10 Comeau, W. J., Hamilton, J. G. M., and White, P. D. Paroxysmal Bundle-Branch Block Associated with Heart Disease, *Am Heart J* **15** 276, 1938.

*Treatment of Cardiac Arrhythmias*—Fahr<sup>11</sup> has summarized the present status of the treatment of common cardiac irregularities. New material has not been presented, but his paper may be read with profit by all those desiring information on this subject.

#### CONGENITAL HEART DISEASE

In addition to the articles herewith reviewed, the interested reader may refer to other reports,<sup>12</sup> which can be mentioned here only by title.

Patten<sup>13</sup> has written an excellent paper describing the various types of developmental defects encountered at the foramen ovale. He has begun with a summary of the normal prenatal and postnatal development of the interatrial septums, an understanding of which is necessary for the appreciation of what follows. In the separation of the primitive common atrium into right and left chambers, two septums are directly involved, which are termed septum primum and septum secundum on the basis of their sequential appearance. The septum primum, starting as a crescentic ridge on the dorsocephalic part of the atrial wall, grows toward the atrioventricular canal. About the time it seems as if the septum primum would shut off the left atrium from the right, a secondary opening develops near its origin from the dorsocephalic wall. The appearance of this second ostium is of fundamental functional significance, as it allows balanced atrial intakes and prevents defective development of the left side of the heart. About this time the septum secundum begins to develop just to the right of the septum primum. It does not become a complete partition but leaves a characteristic oval aperture, which is the foramen ovale. The remaining portion of the septum primum lies as a loose flap over the foramen ovale and acts as a one way valve, permitting flow only from right to

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11 Fahr, G. The Treatment of Cardiac Irregularities, *J A M A* **111** 2268 (Dec 17) 1938.

12 Manchester, B., and White, P. D. Dextrocardia with Situs Inversus Complicated by Hypertensive and Coronary Heart Disease, *Am Heart J* **15** 493, 1938. Krumbhaar, E. B., and Ehrlich, W. E. Varieties of Single Coronary Artery in Man, Occurring as Isolated Cardiac Anomalies, *Am J M Sc* **196** 407, 1938. Lev, M., and Saphir, O. Congenital Aneurysm of the Membranous Septum, *Arch Path* **25** 819 (June) 1938. Oppenheimer, E. H. Partial Atresia of the Main Branches of the Pulmonary Artery Occurring in Infancy and Accompanied by Calcification of the Pulmonary Artery and Aorta, *Bull Johns Hopkins Hosp* **63** 261, 1938. Gibson, S., and Clifton, W. M. Congenital Heart Disease. A Clinical and Postmortem Study of One Hundred and Five Cases, *Am J Dis Child* **55** 761 (April) 1938. Graybiel, A., Strieder, J. W., and Boyer, N. H. An Attempt to Obliterate the Patent Ductus Arteriosus in a Patient with Subacute Bacterial Endarteritis, *Am Heart J* **15** 621, 1938.

13 Patten, B. M. Developmental Defects at the Foramen Ovale, *Am J Path* **14** 135, 1938.



left Following birth there is a gradual diminution of the interatrial communication, and at the end of a month the foramen ovale is functionally closed, although a probe may be freely passed During the next six to eight months the flaplike valve is converted into a fixed septal structure, and later fibrous adhesion of the valvula to the septum occurs In 20 to 25 per cent of adults the fibrous adhesion is never entirely completed Such failures of complete adhesion appear to be of no functional significance and may be regarded as variations of the normal rather than as abnormalities, although in the event of disturbances in the pulmonary circuit an area of incomplete adhesion may again become a path for transseptal flow

Patten believes that pathologic lesions rarely, if ever, appear to play a part in the primary causation of a developmental septal defect but that these defects are the result of "developmental arrests" and abnormalities in the normal process of resorption of tissue The most common type of defect at the foramen ovale is that in which there has been just a little too much resorption of the septum primum, leading to failure of the valvula to overlap the foramen completely Cases have been presented in which abnormal interatrial openings appeared as the result of

(1) underdevelopment of septum secundum, (2) resorption of septum primum starting in the normal location but going too far, (3) resorption of septum primum taking place in abnormal locations, and (4) overgrowth of septum secundum

The author has emphasized the necessity of discriminating more critically between an open foramen ovale with a competent but unfused valve and a frankly unguarded (patent) foramen ovale In the former instance, leakage, if it occurs, is only from the right to the left, and crossed emboli are comparatively frequent In the widely patent foramen ovale the conditions are much the same if there is associated pulmonary stenosis, because the transseptal flow is from right to left But when pulmonary stenosis is absent the interatrial flow is from left to right and may produce a well recognized clinical picture In contrast with certain other types of congenital defects, subacute bacterial endocarditis is strikingly absent, and chronic pericardial disease, crossed embolism and pulmonary tuberculosis are noticeably rare concomitants

Barclay and Franklin,<sup>14</sup> using direct roentgen cinematography combined with injection of colloidal thorium dioxide, found that the foramen ovale remained patent after functional closure of the ductus arteriosus

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14 Barclay, A. E., and Franklin, K. J. The Time of Functional Closure of the Foramen Ovale in the Lamb, *J. Physiol.* **94** 256, 1938

in lambs delivered by cesarean section. The latest time at which evidence of such patency was obtained was six minutes and forty seconds after delivery.

Taussig and her co-workers<sup>15</sup> have reported 4 cases of interauricular septal defects and have discussed the clinical and pathologic data. The essential pathologic features are a widely patent foramen ovale, great dilatation and hypertrophy of the right auricle and the right ventricle, relative enlargement of the pulmonary artery and a small left ventricle and aorta. The significant findings on physical examination are deformity of the left side of the chest of a frail person, marked cardiac enlargement to the right and usually a harsh systolic murmur and thrill in the second and third left interspaces. Clubbing and cyanosis are absent. Common sequelae are cardiac arrhythmias, superimposed rheumatic infections, pulmonary infections, paradoxical emboli and freedom from subacute bacterial endocarditis.

Barclay and his associates,<sup>16</sup> in order to find out more definitely the time and manner of closure of the ductus arteriosus, succeeded in obtaining roentgenographic records of the ductus in full term lambs immediately after cesarean section. The injection of thorium dioxide was begun within thirty seconds after delivery, and serial records were taken at the rate of about one a second. It was found that the flow of blood through the ductus is sluggish as early as twenty-five seconds after delivery and that functional closure is complete within the first minute. Closure is not the result of a simple contraction of the walls of the ducts but of twisting and kinking of the lumen and is unrelated either to interruption of the maternal circulation or to the lamb's respiration.

Taussig,<sup>17</sup> in a classic paper, has described the clinical and pathologic features of complete transposition of the great vessels in 4 cases, emphasizing the clinical signs by which this anomaly can be recognized during life. She points out that the fundamental feature in these cases is the abnormal torsion of the aortic septum, whereby the aorta arises from the right ventricle and the pulmonary artery from the left ventricle. In order that this malformation may be compatible with life, even for a short time, there must be an additional malformation which permits some crossing of the systemic and pulmonary circulations. The problem resolves itself into the recognition of the transposition and an

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15 Taussig, H. B., Harvey, A. M., and Follis, R. H., Jr. The Clinical and Pathological Findings in Interauricular Septal Defects. A Report of Four Cases, *Bull. Johns Hopkins Hosp.* **63**: 61, 1938.

16 Barclay, A. E., Barcroft, J., Barron, D. H., and Franklin, K. J. X-Ray Studies of the Closing of the Ductus Arteriosus, *Brit. J. Radiol.* **11**: 570, 1938.

17 Taussig, H. B. Complete Transposition of the Great Vessels, *Am. Heart J.* **16**: 728, 1938.

analysis of the concomitant malformations. In regard to the former, Taussig found that the diagnosis is based primarily on the changes in the shadow cast by the great vessels, combined with persistent cyanosis. In the anteroposterior view of the heart the shadow cast by the great vessels is narrow because the pulmonary artery lies directly behind the aorta, in the left anterior oblique view the two vessels lie parallel, and the shadow cast by these vessels is abnormally wide. The shape of the heart is also suggestive, especially enlargement of the right ventricle and absence of the shadow cast by the pulmonary conus. The electrocardiogram may or may not be of aid in the recognition of right ventricular enlargement.

#### RHEUMATIC HEART DISEASE

*Etiology*—During the past few years some evidence has been presented suggesting the possibility that rheumatic fever is due to a virus infection. This work, which has been summarized in previous reviews, revealed that suspensions of particles bearing a close resemblance to elementary bodies of known virus infection can be prepared from exudates from patients with acute rheumatic fever, rheumatoid arthritis and chorea. These particles were found to be agglutinated by serum from patients suffering from the corresponding disease, whereas various control suspensions were not agglutinated. Although these observations were not confirmed by all workers, it was only reasonable that the infectivity of these virus-like bodies should be tested.

Eagles and his co-workers<sup>18</sup> have made such tests by preparing suspensions of virus-like bodies from a variety of materials from rheumatic patients and testing them for infectivity in monkeys both alone and in combination with streptococcus toxin and streptococci. As a result of the inoculations in certain instances the clinical behavior suggested possible cardiac damage, but this was not supported by the pathologic data. The authors, while recognizing the limitations of their study, concluded that no evidence has been obtained that the suspensions of the virus-like bodies possess infectivity.

*Pathologic Features*—The pulmonary changes in acute rheumatic fever and in chronic rheumatic heart disease<sup>19</sup> are becoming better

18 Eagles, G. H., Evans, P. R., Keith, J. D., and Fisher, A. G. T. Infection Experiments with Virus-Like Bodies from Rheumatism, *J. Path. & Bact.* **46**: 481, 1938.

19 Gouley, B. A. The Role of Mitral Stenosis and of Post-Rheumatic Pulmonary Fibrosis in the Evolution of Chronic Rheumatic Heart Disease, *Am. J. M. Sc.* **196**: 11, 1938. The Evolution of the Parenchymal Lung Lesions in Rheumatic Fever and Their Relationship to Mitral Stenosis and Passive Congestion, *ibid.* **196**: 1, 1938. Melnick, P. J. Pulmonary Changes in Rheumatic Fever, *Illinois M. J.* **73**: 336, 1938. Hadfield, G. The Rheumatic Lung, *Lancet* **2**: 710, 1938.

understood, and their clinical significance is being better appreciated. Of particular interest are Gouley's observations that in some patients with mitral stenosis the essential cause of heart failure is not valvular obstruction but rather an important and independent structural change in the lung. He believes that this phenomenon is in the beginning a direct result of rheumatic fever, the pneumonitis leading often to widespread fine interstitial fibrosis which may, after inflammatory recurrences, become progressively more severe. This he believes may play an important role in the causation of heart failure.

*Clinical Features*—There has never been general agreement among clinicians regarding the value of tonsillectomy in cases of rheumatic heart disease, and recent reports<sup>20</sup> have not brought agreement any nearer. However, the evidence does indicate that tonsillectomy should not ordinarily be attempted during the acute or the subacute phase of rheumatic infection and that tonsillectomy does not prevent the recurrences of rheumatic manifestations. It does indicate that tonsillectomy in the case of a rheumatic patient who does not have cardiac involvement at the time of operation should be recommended, since it may aid in the prevention of rheumatic heart disease.

Taussig and Hecht<sup>21</sup> have reported 37 cases in which hypertension occurred in close association with an acute rheumatic episode in childhood. Demonstrable renal damage was not associated with the hypertension in any of these cases. Various possibilities are discussed, but the exact relation between the hypertension and the rheumatic infection is not clear. Salvesen's<sup>22</sup> account of 6 cases of "rheumatic nephritis" is interesting in this connection. These 6 cases were found among 287 cases of nephritis, and, in addition, a survey of 212 cases of rheumatic fever revealed acute nephritis to be present in 10 instances. Whether this represents more than a chance association is unknown. It is pointed out that infection of the upper respiratory tract sometimes precedes glomerulonephritis, just as it commonly precedes rheumatic fever.

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20 Allan, W. B., and Baylor, J. W. The Influence of Tonsillectomy upon the Course of Rheumatic Fever and Rheumatic Heart Disease. Study of One Hundred and Eight Cases, *Bull. Johns Hopkins Hosp.* **63** 111, 1938. Ash, A. Influence of Tonsillectomy on Rheumatic Infection, *Am. J. Dis. Child.* **55** 63 (Jan.) 1938. Turnley, W. H. Tonsillectomy for Rheumatism. Study of 3,172 Cases, *Ann. Otol., Rhin. & Laryng.* **46** 1050, 1938.

21 Taussig, H. B., and Hecht, M. S. Studies Concerning Hypertension in Childhood. II. The Occurrence of Hypertension in Acute Rheumatic Fever in Childhood, *Bull. Johns Hopkins Hosp.* **62** 491, 1938.

22 Salvesen, H. A. Rheumatic Fever and Nephritis, *Acta med. Scandinav.* **96** 304, 1938.

Keil<sup>23</sup> has written a comprehensive monograph on rheumatic subcutaneous nodules. He believes this term should be applied only to lesions occurring in the course of undoubted rheumatic fever. Pathologically, these nodules present certain well recognized characteristics, but these characteristics are not pathognomonic. They consist essentially of small unit areas, grossly visible to the naked eye as millet-sized bodies and microscopically divisible into an inner necrobiotic core, a middle cellular layer and a peripheral zone showing increased vascularity. He has arbitrarily separated the discussion of the rheumatic nodules seen in children and those seen in adults. In adults there is a tendency for these lesions to show atypical localization, their incidence is small and their diagnostic value is impaired because of the opportunities for confusing them with other lesions. In children the rheumatic nodule is considered by Keil to be highly specific of rheumatic fever, and evidence has been given by him that the heart is "practically" always affected concurrently in one form or another. The typical nodule in rheumatoid arthritis is thought to differ from that in rheumatic fever in many clinical attributes and in some pathologic respects. In this connection McEwen,<sup>24</sup> using a supravital staining technic, found that the cells of rheumatoid arthritis nodules have essentially the same characteristics as those of rheumatic fever.

Keil<sup>25</sup> has presented a critical survey of rheumatic erythemas based on 53 examples discovered among 523 cases of rheumatic disease. These erythemas comprised several varieties, which have been classified as follows:

- 1 Simple papular form
- 2 Ringed forms
  - (a) Erythema marginatum rheumaticum
  - (b) Flat annular erythema

Each group has been considered separately, and this includes a description of the erythema, with its clinical attributes and its relation to active rheumatic disease.

Bland and Jones<sup>26</sup> have analyzed the fatal course of rheumatic fever and its sequelae in 306 young patients. Rheumatic fever was directly

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23 Keil, H. The Rheumatic Subcutaneous Nodules and Simulating Lesions, *Medicine* **17** 262, 1938.

24 McEwen, C. Cytologic Studies on Rheumatic Fever. III. A Comparison of Cells of Subcutaneous Nodules from Patients with Rheumatic Fever, Rheumatoid Arthritis and Syphilis, *Arch. Path.* **25** 303 (March) 1938.

25 Keil, H. The Rheumatic Erythemas. A Critical Survey, *Ann. Int. Med.* **11** 2223, 1938.

26 Bland, E. F., and Jones, T. D. Fatal Rheumatic Fever, *Arch. Int. Med.* **61** 161 (Feb.) 1938.

responsible for the fatality in 250 instances. It was found that the age of onset was not significant but that the early years after the onset of the disease often proved to be a critical period. In the majority the fatal illness usually extended over several months and represented an exacerbation of long-standing and clinically recognizable rheumatic fever. Aside from the general clinical picture, certain features were of particular interest. Arthritis was not present in any case, although variable arthralgia causing some discomfort was present in about half the group. Chorea was encountered in only 2 instances during the terminal illness. Carditis was present in every patient and was manifested clinically by marked cardiac enlargement, tachycardia, characteristic murmurs and ultimate failure of the congestive type. Evidence of involvement of the lung and liver was frequently observed.

Boone and Levine<sup>27</sup> have studied the prognosis for 225 young patients with "potential rheumatic heart disease" and "rheumatic mitral insufficiency" followed for an average of 9.6 years. Of the former, about 5 per cent subsequently had mitral stenosis, aortic insufficiency or both. Of those with "mitral insufficiency," about 42 per cent subsequently had mitral stenosis or aortic insufficiency, while 58 per cent remained unchanged.

Keith<sup>28</sup> has presented further evidence that prolongation of the auriculoventricular conduction time, which is the most characteristic abnormality in the electrocardiogram of patients suffering from rheumatic heart disease, is due to overstimulation of the vagus nerve. He found the average PR interval to be 0.138 second, with a range of 0.12 to 0.17 second, in 26 children without heart disease, which agrees closely with figures reported by other investigators. Serial electrocardiograms of 200 patients with various rheumatic manifestations showed that the average maximum PR interval was much greater than the normal average, although the highest averages were observed when carditis was present. After the administration of atropine to 11 rheumatic children with a PR interval of 0.19 second or over, the average reduction in conduction time was 0.048 second, which is much greater than the average reduction of 0.013 second observed in a control group. From this and other supporting evidence Keith has concluded that overstimulation of the vagus nerve is present in acute rheumatic fever and that it is probably the result of direct overactivity of the nerve endings in the heart.

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27 Boone, J. A., and Levine, S. A. The Prognosis in "Potential Rheumatic Heart Disease" and "Rheumatic Mitral Insufficiency." *Am J M Sc* **195** 764, 1938.

28 Keith, J. D. Over-Stimulation of the Vagus Nerve in Rheumatic Fever, *Quart J Med* **7** 29 1938.

*Treatment*—Because of the relation between infections due to beta hemolytic streptococci and rheumatic fever, it was logical to try the effect of sulfanilamide in both the prevention and the treatment of the rheumatic attack. There have been many verbal and a few written reports<sup>29</sup> of its use. A few conclusions may be tentatively drawn, although more time is needed before a final evaluation can be safely made. Not only does sulfanilamide apparently fail to have any beneficial effect on the course of rheumatic fever, but, as a result of its use, certain rheumatic features may become manifest. Furthermore, the toxic effects of the drug are especially marked in these patients. On the other hand, when sulfanilamide (15 to 20 grains [0.97 to 1.29 Gm.] daily) was given continuously during the course of two winters to 30 patients with a recent history of acute rheumatic fever, none had any illness in which the diagnosis of rheumatic fever was brought into question. Thus it appears that sulfanilamide is contraindicated in acute rheumatic fever but may have a place in prophylaxis.

#### ARTERIAL HYPERTENSION

*Pathogenesis*—Studies on experimental hypertension<sup>30</sup> continue to represent the most important advances being made in the field of

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29 Swift, H. F., Moen, J. K., and Hirst, G. K. The Action of Sulfanilamide in Rheumatic Fever, *J. A. M. A.* **110** 426 (Feb. 5) 1938. Massell, B. F., and Jones, T. D. The Effect of Sulfanilamide on Rheumatic Fever and Chorea, *New England J. Med.* **218** 876, 1938. Thomas, C. B., and France, R. A Preliminary Report of the Prophylactic Use of Sulfanilamide in Patients Susceptible to Rheumatic Fever, *Bull. Johns Hopkins Hosp.* **64** 67, 1939.

30 Goldblatt, H. Experimental Hypertension Induced by Renal Ischemia, in *Harvey Lectures, 1937-1938*, Baltimore, Williams and Wilkins Company, 1938, p. 237. Dicker, E. Recherches experimentales concernant le mécanisme de l'hypertension d'origine renale chez le chien, *Arch. internat. de med. exper.* **13** 27, 1938. Fasciolo, J. C., Houssay, B. A., and Taquino, A. C. The Blood Pressure Raising Secretion of the Ischaemic Kidney, *J. Physiol.* **94** 281, 1938. Williams, J. R., Jr., Harrison, T. R., and Mason, M. F. Observations on Two Different Pressor Substances Obtained from Extracts of Renal Tissue, *Am. J. M. Sc.* **195** 339, 1938. Merrill, A., Williams, J. R., Jr., and Harrison, T. R. The Site of Action of the Renal Pressor Substance, *ibid.* **196** 18, 1938. Merrill, A., Williams, R. H., and Harrison, T. R. The Effects of a Pressor Substance Obtained from the Kidneys on the Renal Circulation of Rats and Dogs, *ibid.* **196** 240, 1938. Child, C. G. Observations on the Pathological Changes Following Experimental Hypertension Produced by Constriction of the Renal Artery, *J. Exper. Med.* **67** 521, 1938. Pickering, G. W., and Prinzmetal, M. Some Observations on Renin, a Pressor Substance Contained in Normal Kidney, Together with a Method for Its Biological Assay, *Clin. Sc.* **3** 211, 1938. Boyd, J. D., and McCullagh, G. P. Experimental Hypertension Following Carotico-Aortic Denervation in the Rabbit, *Quart. J. Exper. Physiol.* **27** 293, 1938. Levy, S. E., and Blalock, A. Experimental Attempts to Prevent or Abolish Hypertension That Is Associated with

cardiovascular disease. The literature on this subject has increased to such an extent that a detailed summary is no longer within the scope of this review.

The revival of interest in experimental hypertension is largely due to Goldblatt and his co-workers, who have shown that in the dog permanent hypertension may follow constriction of the renal arteries. There has followed an impressive series of experiments by many workers designed to interpret the exact nature of this phenomenon.

The association of hypertension with renal disease has long been known but has always been attributed to the diminution of the excretory power of the kidney which allowed the retention of substances normally eliminated. Recent studies have shown, however, that renal hypertension may be produced in dogs without significantly decreasing the renal function. In fact, procedures which allow retention of renal excretory products, such as removing most or all of the renal substance or anastomosing a ureter to an iliac vein, do not produce hypertension. Experimental hypertension may follow the constriction of the renal arteries but cannot be produced unless the kidneys are present and unless they are irrigated with blood.

The hypertensive action of the ischemic kidney is independent of the action of the endocrine glands except so far as these glands are necessary to the maintenance of the body in a responsive state.

It has also been demonstrated that the nervous system does not play an essential role in the development of renal hypertension, since

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Renal Ischemia, Surgery **3** 899, 1938. Page, I. H. The Effect of Bilateral Adrenalectomy on Arterial Blood Pressure of Dogs with Experimental Hypertension, *Am J Physiol* **122** 352, 1938. Collins, D. A., and Wood, E. H. Experimental Renal Hypertension and Adrenalectomy, *ibid* **123** 224, 1938. MacKay, L. L., Addis, T., and MacKay, E. M. The Degree of Compensatory Renal Hypertrophy Following Unilateral Nephrectomy. II. The Influence of the Protein Intake, *J Exper Med* **67** 515, 1938. Verney, E. B., and Vogt, M. An Experimental Investigation into Hypertension of Renal Origin, with Some Observations on Convulsive "Uraemia," *Quart J Exper Physiol* **28** 253, 1938. Enger, R., Linder, F., and Sarre, H. Die Wirkung quantitativ abgestufter Drosselung der Nierendurchblutung auf den Blutdruck, *Ztschr f d ges exper Med* **104** 1, 1938. Glenn, F.; Child, C. G., and Page, I. H. The Effect of Destruction of the Spinal Cord on Hypertension Artificially Produced in Dogs, *Am J Physiol* **122** 506, 1938. Glenn, F., and Lasher, E. P. The Effect of Destruction of the Spinal Cord on the Artificial Production of Hypertension in Dogs, *ibid* **124** 106, 1938. Child, C. G., and Glenn, F. Effect of Passing Renal Blood Through Liver in Dogs with Experimental Hypertension, *Arch Surg* **36** 376 (March) 1938. Wilson, C., and Pickering, G. W. Acute Arterial Lesions in Rabbits with Experimental Renal Hypertension, *Clin Sc* **3** 343, 1938. Goldblatt, H. Studies on Experimental Hypertension. VII. The Production of the Malignant Phase of Hypertension, *J Exper Med* **67** 809, 1938. Katz, L. N., Mendlowitz, M., and Friedman, M. A Study of the Factors Concerned in Renal Hypertension, *Proc Soc Exper Biol & Med* **37** 722, 1938.



deneivation of the kidneys, total sympathectomy or destruction of the cord below the level of the fifth cervical vertebra does not prevent its development. Furthermore, constriction of the renal artery of a transplanted kidney, free from all nervous connections, leads to an increase in blood pressure.

On the other hand, many experiments are in accord with the fact that renal hypertension is brought about by the liberation of some pressor body by the ischemic kidney.

The search for this pressor substance elaborated by the kidneys goes back forty years to the work of Tigerstedt and Bergman, who demonstrated in extracts of normal kidney a pressor substance to which they gave the name renin. Although this was a major discovery and received some confirmation, it attracted little attention because various investigators, in repeating the tests, obtained doubtful or inconsistent results. There were two chief reasons for this. First, many of the early experiments were carried out on anesthetized animals, and it has been recently shown that the pressor effect of renin is reduced or abolished by anesthetics such as ethyl carbamate (urethane), pentobarbital and ether. Secondly, in preparing renal extracts, precautions must be taken to remove certain depressor substances, or the pressor action of renin will be masked. Better methods have been developed for the removal of depressor substances, and renal extracts can now be prepared which consistently show a good pressor action.

Pickering has stated that renin appears to be a normal constituent of the renal cortex of various animals. In its properties it resembles a protein and is distributed between the euglobulin and pseudoglobulin protein fractions. It is nondialyzable and in neutral solution is destroyed at 60 C. It is insoluble in alcohol, acetone, ether and chloroform and is precipitated by half saturation with ammonium sulfate.

There is some evidence that extracts prepared from ischemic kidneys have a greater pressor action than extracts from normal kidneys. If confirmed, this is important because it suggests that in the ischemic kidney renin is being elaborated in larger amounts. Of greater importance would be the recovery of renin from the circulating blood and demonstration that it is increased in amount when hypertension is present.

There is additional support for the idea that a humoral mechanism is responsible for arterial hypertension in the experiments of Pickering, Prinzmetal and Wilson. They have demonstrated in patients with arterial hypertension that excessive narrowing of the vessels of the hands still remains after removal of vasoconstrictor tone. This strongly suggests that vasoconstriction of humoral origin is present, which dovetails with the results of the studies on experimental hypertension.

Other supporting evidence comes from studies<sup>31</sup> on coarctation of the aorta. In some cases of coarctation, in addition to hypertension in the upper extremities, there is diastolic hypertension in the lower extremities, which indicates a generalized increase in peripheral resistance. Now, it has also been shown<sup>32</sup> that if the aorta of the rat is partially constricted above the point of origin of the renal arteries, hypertension results. This suggests a similarity between the hypertension observed in the patient with coarctation and the hypertension in the rat with constriction of the aorta.

*Pressor Responses in Patients with Hypertension*—A number of papers<sup>33</sup> have appeared concerning the effect of various substances or stimuli upon the blood pressure. Of particular interest are the observations of Alam and Smirk. Previously they showed that exercise of the muscles of the forearm performed during arrest of the circulation of the blood to the forearm leads to a rise in the general blood pressure as well as to the production of pain in the exercised muscles. They showed that the rise in blood pressure is reflex in origin and that a definite increase often appears before pain arises. This led to further studies and to an evaluation of the relation between pain of various types and increase in the blood pressure. They found that some sensory stimuli cause much pain but little rise of blood pressure, while others cause less pain but much greater increases of blood pressure. Using cold and exercise of an ischemic limb as stimuli, they studied the blood pressure responses in patients with hypertension and in normal subjects. They found that the effects on both systolic and diastolic pressures are less in patients with renal hypertension than in normal subjects of the same age group. Marked effects on blood

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31 Steele, J. M., and Cohn, A. E. The Nature of Hypertension in Coarctation of the Aorta, *J. Clin. Investigation* **17** 514, 1938.

32 Rytand, D. A. The Renal Factor in Arterial Hypertension with Coarctation of the Aorta, *J. Clin. Investigation* **17** 391, 1938.

33 Alam, M., and Smirk, F. H. Observations in Man Concerning the Effects of Different Types of Sensory Stimulation upon the Blood Pressure, *Clin. Sc.* **3** 253, 1938, Blood Pressure Raising Reflexes in Health, Essential Hypertension, and Renal Hypertension, *ibid.* **3** 259, 1938. Fatheree, T. J., and Hines, E. A. The Blood Pressure Response to Epinephrine Administered Intravenously to Subjects with Normal Blood Pressure and to Patients with Essential Hypertension, *Am. Heart J.* **16** 66, 1938. Ayman, D., and Goldshine, A. D. Cold as a Standard Stimulus of Blood Pressure. A Study of Normal and Hypertensive Subjects, *New England J. Med.* **219** 650, 1938. Hardgrove, M., Roth, G. M., and Brown, G. E. The Pressor Reaction Produced by Inhalation of Carbon Dioxide. Studies of Patients with Normal Blood Pressure and with Hypertension, *Ann. Int. Med.* **12** 482, 1938. Elsom, K. A., and Glenn, P. M. The Pressor Response of Normal and Hypertensive Human Subjects to Tyramine Introduced into the Ileum, *ibid.* **12** 838, 1938.

pressure were found to occur more frequently in patients with essential hypertension than in normal controls of the same age. Sometimes, however, large rises in blood pressure occurred in normal subjects and small rises in patients with essential hypertension. They concluded that essential hypertension does not usually develop subsequently in healthy subjects with a high reflex reactivity of the blood pressure.

*Hypertension in the Pulmonary Circuit*—Staemmler<sup>34</sup> has speculated on the possibility that primary hypertension in the lesser circulation may be the cause of hypertrophy of the right ventricle which cannot otherwise be explained. In regard to thromboendarteritis obliterans, a disorder characterized by the formation and organization of fibrinoid thrombi in the small pulmonary arteries, he arrived at the conclusion that primary hypertension in the lesser circulation must be regarded as the cause. He has also suggested that many instances of pulmonary sclerosis may be due to the same cause. An important argument against this idea, however, is the considerable difference anatomically between the pulmonary and the systemic circulation, there being absent from the former the characteristic arterioles, spasm of which in the latter is probably responsible for the first stage of "primary hypertension."

*Treatment*—There are further reports<sup>35</sup> on the surgical treatment of so-called essential hypertension. In general, these reports are optimistic. Undoubtedly the "best results" are obtained in comparatively young persons with variable blood pressure who have not yet exhibited marked vascular changes. In these cases it is to be expected that sympathectomy will cause a fall in blood pressure, as vasoconstriction of nervous (sympathetic) origin constitutes a large fraction of the total peripheral resistance. However, as has been outlined, there is

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34 Staemmler, M. Gibt es eine primäre Hypertonie im kleinen Kreislauf? (Zugleich ein Beitrag zur Frage der sogenannten primären Pulmonal-Sklerose), *Arch f Kreislaufforsch* **3** 125, 1938.

35 Crile, G. *The Surgical Treatment of Hypertension*, Philadelphia, W. B. Saunders Company, 1938. Page, I. H. Medical Aspects of Surgical Treatment of Hypertension, *J A M A* **110** 1161 (April 9) 1938. Goldblatt, H. Experimental Observations on the Surgical Treatment of Hypertension, *Surgery* **4** 483, 1938. Rogoff, J. M., and Marcus, E. Supposed Role of the Adrenals in Hypertension. An Experimental Investigation, *J A M A* **110** 2127 (June 25) 1938. Craig, W. M. Hypertension and Its Surgical Treatment, *South Surgeon* **7** 140, 1938. Allen, E. V., and Adson, A. W. Physiologic Effects of Extensive Sympathectomy for Essential Hypertension. Further Observations, *Ann Int Med* **11** 2151, 1938. Paliard, F., and Martin, P. E. Le traitement chirurgical de l'hypertension artérielle permanente. Ses indications par l'infiltration anesthésique des splanchniques, *J de med de Lyon* **19** 433, 1938. Davis, L., and Barker, M. H. The Surgical Problem of Hypertension, *Ann Surg* **107** 899, 1938. Lauter, S., and Ott, A. Ueber die Wirkung des Aderlasses beim Hochdruck, *Deutsches Arch f klin Med* **181** 139, 1937.

increasing evidence to show that the abnormal factor in peripheral resistance is probably hormonal, which limits the rationale of the surgical treatment of hypertension to merely a means of removing part of the normal vasomotor control mechanism. Nevertheless, if its usefulness can be proved empirically, it may remain a valuable measure in selected cases.

Massie, Ethridge and O'Hare,<sup>36</sup> in another revival of the thiocyanate therapy, administered the sodium salt according to the method of Barker to 14 patients with hypertension. Barker's method consists essentially in the use of blood cyanate determinations as a guide to proper administration of the drug. Massie and his associates confirmed Barker's favorable results and obtained a significant lowering of blood pressure when the cyanate level of the blood was kept between 5 and 7 mg per hundred cubic centimeters. Even so, toxic symptoms are occasionally observed, and this method requires careful selection, observation and care of the patient.

#### BACTERIAL ENDOCARDITIS

The use of sulfanilamide or related compounds in the treatment of subacute bacterial endocarditis is a subject of considerable interest at present. Some verbal reports are very encouraging and provide the basis for new hope. Unfortunately the old difficulty is still present, namely, the inability of any therapeutic agent to reach the living bacteria, which are protected by the mass of fibrin and the corpuscular and bacterial debris which constitute the vegetations. Temporarily the blood stream may be sterilized and a remission of symptoms effected with sulfanilamide, but it is unlikely that more than an occasional cure will result. There is some promise that sulfanilamide may be valuable in gonococcic and pneumococcic endocarditis.

Miles and Gray<sup>37</sup> have described 2 cases of infective endocarditis apparently due to *Haemophilus parainfluenzae* and have summarized other cases reported in the medical literature in which there may have been a similar pathogenesis. In these cases preexisting valvular damage to the heart has been seldom absent, and the clinical course and autopsy observations do not differ significantly from those in cases of endocarditis due to *Streptococcus viridans*.

Martin and Adams<sup>38</sup> have described 5 cases of proved syphilitic endocarditis or aortitis with superimposed bacterial vegetations. In

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36 Massie, E., Ethridge, C. B., and O'Hare, J. P. Thiocyanate Therapy in Vascular Hypertension, *New England J Med* **219** 736, 1938.

37 Miles, A. A., and Gray, J. *Haemophilus Para-Influenzae* Endocarditis, *J Path & Bact* **47** 257, 1938.

38 Martin, H. E., and Adams, W. L., Jr. Bacterial Endocarditis Superimposed on Syphilitic Aortitis and Valvulitis, *Am Heart J* **16** 714, 1938.

none of these cases were both diagnoses made clinically, but this combination should be considered whenever sepsis of undetermined origin, a positive Wassermann reaction and evidence of aortic insufficiency or of aortitis without evidence of previous rheumatic infection are present

Recent work<sup>39</sup> on experimental endocarditis has shown that streptococcic endocarditis can be regularly produced in animals and that the infection persists because the surrounding deposits of fibrin afford not only protection from phagocytic cells but an excellent medium for growth. No evidence was observed that the bacterium acquires resistance to the action of white blood cells or that the latter lose their power to destroy the organism.

#### HEART DISEASE DUE TO CORONARY ARTERIOSCLEROSIS

*Pathogenesis*—Moore and his associates<sup>40</sup> have observed a deposition of calcium salts in the yellow elastic fibers of the heart and great vessels of calves fed rations low in magnesium. While these lesions are not typical of arteriosclerotic lesions seen in man, the difference may be due partly to species difference in reaction and to the acuteness of the experiments. They have pointed out that from what is known regarding human requirements for magnesium, deficiency of this element commonly exists in man.

Handovsky<sup>41</sup> fed large amounts of vitamin D to normal dogs and to dogs from which the thyroid and parathyroid glands had been removed. In the latter, macroscopic sclerotic lesions appeared in the aorta, whereas in the former none appeared. When thyroid was given to thyroparathyroprivic dogs, lesions did not appear, which shows the importance of the thyroid function in this regard.

*Angina Pectoris*—Starr and his collaborators<sup>42</sup> have made estimations of cardiac output, basal metabolic rate, pulse rate and respiratory rate during and between attacks of angina pectoris. Their results

39 Friedman, M., Katz, L. N., and Howell, K. Experimental Endocarditis Due to *Streptococcus Viridans*. Biologic Factors in Its Development, *Arch Int Med* **61** 95 (Jan.) 1938. Kinsella, R. A., and Muether, R. O. Experimental Streptococcic Endocarditis, *ibid* **62** 247 (Aug.) 1938. Friedman, M. A Study of the Fibrin Factor in Its Relation to Subacute Endocarditis, *J Pharmacol & Exper Therap* **63** 173, 1938.

40 Moore, L. A., Hallman, E. T., and Sholl, L. B. Cardiovascular and Other Lesions in Calves Fed Diets Low in Magnesium, *Arch Path* **26**:820 (Oct.) 1938.

41 Handovsky, H. Du rôle de la thyroïde et de la parathyroïde dans le développement de l'arteriosclérose, *Schweiz med Wchnschr* **68** 425, 1938.

42 Starr, I., Gamble, C. J., Donal, J. S., and Collins, L. H. Estimations of the Work of the Heart During and Between Attacks of Angina Pectoris, *J Clin Investigation* **17** 287, 1938.

indicate that the work of the heart is significantly greater during the time of the attack and thereby conform to the widely accepted view that cardiac pain is caused by situations demanding increased cardiac work when the blood supply of the heart cannot be increased correspondingly

Robertson and Katz <sup>43</sup> have described a method for inducing attacks of pain in patients with angina pectoris, which consists of placing an ordinary blood pressure cuff on the left arm above the elbow and inflating it to 50 mm of mercury above the systolic blood pressure. The inflation is continued for five minutes or until pain is elicited. The test gave negative results in control subjects but positive results in 19 of 24 patients with a definite history of angina pectoris. The possible mechanisms involved are described, and the usefulness of the test is emphasized.

Reid <sup>44</sup> has observed a series of patients in whom the pressure of a cervical rib or of the scalenus anticus muscle on the brachial plexus has been the cause of pain simulating that of angina pectoris. Even precordial pain may be so induced, and some relation to exertion may be manifest. It is pointed out that this syndrome is not rare and that it is important to differentiate it from angina pectoris or coronary thrombosis.

O'Shaughnessy and his associates <sup>45</sup> have described their further experience with cardio-omentopexy. In this procedure a left transpleural exposure of the heart is made, and the left side of the diaphragm is paralyzed by means of crushing the phrenic nerve. An opening is then made in the diaphragm, and a pedicled graft of omentum is brought up and attached to the heart. It has been demonstrated in experimental animals that vascular communications can develop between the omentum and the heart. Twenty patients have been operated on, 15 were suffering from angina pectoris and 5 from other symptoms due to cardiac ischemia. Of the 15 patients who had angina pectoris, 10 were alive six months or longer after the operation, 8 of these 10 had lost the angina and most of them were able to resume profitable activity. Of the 5 patients without angina pectoris, 1 died, while 1 of the remaining 4 became free from symptoms. There was 1 death directly attributable to operation, this resulted from rupture of a friable portion of the cardiac wall. Generally, the operation is attended with little shock, and convalescence is uneventful. O'Shaughnessy's encouraging

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43 Robertson, S, and Katz, L. N. Observations on Referred Pain of Cardiac Origin, *Am J M Sc* **196** 199, 1938

44 Reid, W. D. Pressure on the Brachial Plexus Causing Simulation of Coronary Disease, *J A M A* **110** 1724 (May 21) 1938

45 Davies, D. T., Mansell, H. E., and O'Shaughnessy, L. Surgical Treatment of Angina Pectoris and Allied Conditions, *Lancet* **1** 1 and 76, 1938

results with cardio-omentopexy warrant further trial, with careful control studies. The operation may or may not prove to be an advance in the treatment of selected patients with coronary insufficiency.

*Coronary Occlusion*—Coronary thrombosis may be properly regarded as a complication of coronary atherosclerotic disease. Unfortunately, it may occur in persons who present little if any evidence of coronary insufficiency. In other words, these persons might have lived healthy lives for many years if thrombosis with resulting cardiac infarction had not occurred. It is small wonder, then, that great efforts are being made to study not only the underlying atherosclerotic lesion itself but also the various factors connected with thrombosis in a coronary artery. Recent studies embrace the normal vascular supply of large vessels and the development of atheromatous lesions,<sup>46</sup> a new method of studying coronary artery occlusion and anastomoses,<sup>47</sup> the circumstances and precipitating factors under which coronary thrombosis occurs<sup>48</sup> and the problem of "heparin and thrombosis."<sup>49</sup>

Although there is much doubt regarding the vascularity of the intima of normal vessels, there is no doubt about the presence of capillaries in the intima in atherosclerotic lesions, and it has been shown that intimal hemorrhages may result from rupture of capillaries in coronary atherosclerotic lesions. In some instances thrombosis within the lumen of the artery may apparently follow as a secondary effect. However, because intimal hemorrhage occurs so often with complete patency of the adjacent lumen, it is obvious that some additional factor is necessary to initiate thrombosis. It is suggested that this factor is narrowing of the lumen at a point distal to the attachment of the thrombus which provides proper conditions of stagnation and eddying of blood. Paterson considers two principal factors to be involved in the mechanism of capillary rupture, namely, softening by atheroma of the supporting stroma and a high intracapillary pressure. Intimal

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46 Winternitz, M. C., Thomas, R. M., and Le Compte, P. M. *The Biology of Arteriosclerosis*, Springfield, Ill., Charles C. Thomas, Publisher, 1938. Leary, T. Vascularization of Atherosclerotic Lesions, *Am Heart J* **16** 549, 1938.

47 Schlesinger, M. J. An Injection Plus Dissection Study of Coronary Artery Occlusions and Anastomoses, *Am Heart J* **15** 528, 1938.

48 Paterson, J. C. Capillary Rupture with Intimal Hemorrhage as a Causative Factor in Coronary Thrombosis, *Arch Path* **25** 474 (April) 1938. Wartman, W. B. Occlusion of the Coronary Arteries by Hemorrhage into Their Walls, *Am Heart J* **15** 459, 1938.

49 Best, C. H., Cowan, C., and Maclean, D. L. Heparin and the Formation of White Thrombi, *J Physiol* **92** 20, 1938. Solandt, D. Y., and Best, C. H. Heparin and Coronary Thrombosis in Experimental Animals, *Lancet* **2** 130, 1938. Best, C. H. Heparin and Thrombosis, *Brit M J* **2** 977, 1938. Murray, G. D. W., and Best, C. H. Use of Heparin in Thrombosis, *Ann Surg* **108** 163, 1938.

capillaries, because they arise directly from the main coronary lumen, are exposed constantly to a relatively high pressure of blood

Schlesinger has made an important contribution to the study of the anastomoses of normal and diseased coronary vessels. He has described a new method, which consists in cutting the heart so that it can be unrolled and roentgenograms made after the injection of a multicolored opaque medium. In this way the entire course of all the arterial branches can be completely and simultaneously visualized. Schlesinger believes that only in this way is it possible to ascertain accurately the site and the effects of all the occlusions and anastomoses of the coronary arteries. His studies led to the conclusion that the coronary arteries in normal human hearts, even senile hearts, are functionally true end arteries and that anastomotic connections do not develop along with increase in age. He further concluded that anastomoses always develop readily whenever and wherever arteriosclerotic narrowing or occlusion causes obstruction in the coronary circulation.

The recent studies by Best and others on heparin and on blood coagulation are of unusual interest now and may perhaps in the future have great practical importance for the physician and cardiologist. The pure heparin now available is nontoxic and may be administered continuously for days by the intravenous route. It was found that heparin prevented the thrombus formation which normally occurs in the experimental animal after injection of sodium ricinoleate into the lumen of the coronary artery. It is emphasized that the main difficulty in the way of an adequate clinical investigation of the therapeutic possibilities of heparin in acute coronary crises is the absence of premonitory signs of this condition. It is of interest in this connection to note that if coronary thrombosis is usually initiated by capillary hemorrhage, the use of heparin may promote this bleeding as well as act beneficially to prevent thrombus formation. Nevertheless this work stands as a challenge to those interested in this type of heart disease.

There have been a number of papers<sup>50</sup> relating to various clinical aspects of coronary occlusion, a few of which will be briefly reviewed

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50 Master, A. M., Dack, S., and Jaffe, H. L. Postoperative Coronary Artery Occlusion, *J. A. M. A.* **110** 1415 (April 30) 1938. Bean, W. B. Infarction of the Heart. II. Symptomatology of Acute Attack, *Ann. Int. Med.* **11** 2086, 1938, III. Clinical Course and Morphological Findings, *ibid.* **12** 71, 1938. Gorham, L. W., and Martin, S. J. Coronary Occlusion With and Without Pain. Analysis of One Hundred Cases in Which Autopsy Was Done with Reference to the Tension Factor in Cardiac Pain, *Arch. Int. Med.* **62** 821 (Nov.) 1938. Martin, S. J., and Gorham, L. W. Cardiac Pain. An Experimental Study with Reference to the Tension Factor, *ibid.* **62** 840 (Nov.) 1938. Boyd, L. J., and Werblow, S. C. Coronary Thrombosis Without Pain, *Am. J. M. Sc.* **194** 814, 1937. Gold, H.,



Master, Dack and Jaffe have added proof to the opinion, previously expressed, that there is an association between operations on elderly patients with coronary disease and coronary occlusion. They found that the relatively common occurrence of coronary thrombosis post-operatively stands in sharp contrast to its rare occurrence in the medical wards. Consequently, rest in bed alone is not a factor. Shock, tachycardia, dehydration and infection are mentioned as precipitating factors. Their findings suggest that full consideration should be given to all elderly persons in preparation for operation and that special care should be taken to prevent postoperative shock, dehydration and infection.

Bean has made an excellent study of the underlying conditions predisposing to cardiac infarction, the symptoms of acute attacks, the clinical course and the common sequelae.

Martin and Gorham believe that the incidence of coronary occlusion and cardiac infarction without pain may be much higher than is commonly realized. In an analysis of the clinical histories and necropsy data for 100 patients with cardiac infarction, pain was found to be absent in 42 instances. Boyd and Werblow found that one third of their patients with proved coronary thrombosis manifested no pain. Both reports emphasize that elderly patients are more likely not to have pain, this was borne out in the series of Master, Dack and Jaffe, previously mentioned, wherein a large majority of patients did not suffer pain. Gorham and Martin were impressed with the possible role of a tension factor in the production of pain, and some support for this was obtained in an experimental study on animals. However, it is important to note that the more careful and complete the history in cases of coronary thrombosis, the more often pain or oppression (sometimes misleadingly called "shortness of breath" by the patient) is found to have occurred.

Parkinson, Bedford and Thomson<sup>51</sup> have written an excellent article on cardiac aneurysms. They found that cardiac aneurysms, like infarcts, involve the left ventricle almost exclusively and may best be classified as anterior or posterior, according to the coronary branch

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Modell, W., and Travell, J. The Influence of the Size of Cardiac Infarcts upon the Electrocardiogram, *Am Heart J* **15** 77, 1938. Laubry, C., Soulie, P., and Heim de Balsac, R. Le syndrome phreno-gastrique des coronarites, *Arch d mal du cœur* **31** 583, 1938. Nichol, E. S. Large Pericardial Effusion Complicating Acute Coronary Thrombosis, *Ann Int Med* **11** 1900, 1938. Stewart, C. F., and Turner, K. B. A Note on Pericardial Involvement in Coronary Thrombosis, *Am Heart J* **15** 232, 1938. Eppinger, E. C., and Kennedy, J. A. The Cause of Death in Coronary Thrombosis, with Special Reference to Pulmonary Embolism, *Am J M Sc* **195** 104, 1938. Hadorn, W. Ueber kombinierte Thrombo-Embolie der Koronararterien, *Ztschr f Kreislaufforsch* **30** 563, 1938.

51 Parkinson, J., Bedford, D. E., and Thomson, W. A. R. Cardiac Aneurysm, *Quart J Med* **7** 455, 1938.

occluded. Diagnosis depends mainly on roentgenographic examination. Anterior aneurysms, which form the great majority, cause enlargement of the heart to the left, with deformity of its contour. Posterior aneurysms are best seen in the left anterior oblique view and may displace the esophagus.

Among several articles<sup>52</sup> on the electrocardiographic diagnosis of cardiac infarction, that of Wood and Wolferth on infarction of the lateral wall of the left ventricle is of particular interest. The chief electrocardiographic characteristics are depression of the RS-T interval in lead IV and, usually, depression of this interval in leads I and II, together with absence of the signs of posterior infarction in lead III. They have pointed out that in some patients lateral infarction may not be recognized because the electrocardiographic signs of the lesion may disappear rapidly and completely and because the electrocardiographic pattern may be mimicked rather closely by that due to the action of digitalis or to hypertensive heart disease. However, in only 1 of their cases was the diagnosis confirmed at autopsy.

#### HEART DISEASE IN RELATION TO THE ENDOCRINE GLANDS

*Hyperthyroidism*—Ernstene<sup>53</sup> has made a study of cardiovascular complications in 1,000 consecutive patients with hyperthyroidism. Evidence of organic heart disease was present in 173 patients, in 32 additional patients the heart was enlarged, but no other signs of heart disease were found. It was thought that in the great majority of the latter patients the enlargement was due to simple dilatation incident to the thyrotoxicosis. Auricular fibrillation occurred in 207 patients, in 96 of these the arrhythmia was present before operation, while in 111 it developed for the first time as a postoperative complication. Approximately half of the patients with auricular fibrillation presented evidence of organic heart disease, an incidence about five times that observed in the patients without heart disease. Normal sinus rhythm was reestablished spontaneously in one third of the patients with the continuous form of auricular fibrillation. Quinidine sulfate was administered to half the remaining patients in this group, and normal rhythm was restored in 60 per cent. Although the postoperative mortality was considerably greater for patients who had auricular

52 Wood, F. C., Wolferth, C. C., and Bellet, S. Infarction of the Lateral Wall of the Left Ventricle. Electrocardiographic Characteristics, *Am Heart J* **16** 387, 1938. Langendorf, R., and Pick, A. Zur Diagnose des Myokardinfarktes mit Hilfe von Brustwandableitungen, *Acta med Scandinav* **96** 80, 1938. Bohning, A., and Katz, L. N. Four Lead Electrocardiogram in Cases of Recent Coronary Occlusion, *Arch Int Med* **61** 241 (Feb) 1938.

53 Ernstene, A. C. The Cardiovascular Complications of Hyperthyroidism, *Am J M Sc* **195** 248, 1938.

fibrillation, Ernstene has emphasized that this must not be interpreted as evidence that the arrhythmia per se greatly increases the operative risk but that auricular fibrillation is more common in patients who are poor surgical risks

*Myxedema*—Stewart, Detrick and Crane<sup>54</sup> have made interesting and important studies on 4 patients suffering from spontaneous myxedema. They found that the myxedematous state was associated with a low basal metabolic rate, with decrease in cardiac output per minute and per beat, with increase in the arteriovenous oxygen difference and with slowing of the velocity of the blood flow. This was a reversible state, since administration of thyroid was associated with alterations toward the normal levels of these functions and with shrinking of the cardiac size. Of particular interest was their observation that the lengthening of the circulation time in myxedema bears a linear relation to the cardiac output and to the oxygen consumption and that the arteriovenous oxygen difference bears a similar relation to the oxygen consumption and to the basal metabolic rate. Thus it appears that in the myxedematous state, even though the circulatory needs of the body are markedly lowered, the heart does not maintain a circulation adequate for these lowered requirements, and greater amounts of oxygen are removed from each unit of blood than normally occurs. This is discussed in the light of the hypothesis of Boothby and Ryncarson that in the hyperthyroid state there is present in the organism a special circulatory stimulant which causes a greater increase in the circulation rate than occurs in a normal subject as a result of a corresponding increase in oxygen consumption due to work. In the myxedematous state it may be possible that the opposite is the case.

*Acromegaly*—Courville and Mason<sup>55</sup> had occasion to study 24 patients with acromegaly with especial reference to the cardiovascular system both during life and at postmortem examination. In general, the first symptom complained of by these patients is weakness, which is in striking contrast to the great muscular development. As the weakness increases, palpitation and dyspnea on exercise appear and, later, syncopal attacks. As the disease progresses, a striking pallor appears, asthenia becomes extreme, the signs of heart failure increase and finally the patient succumbs. At necropsy the blood vessels are usually enlarged as to both the thickness of the walls and the size of the lumens. The heart may be greatly enlarged, and the enlargement is usually out of proportion to the size of the patient or his muscular

54 Stewart, H. J., Detrick, J. E., and Crane, N. F. Studies on the Circulation in Patients Suffering from Spontaneous Myxedema, *J. Clin. Investigation* **17**: 237, 1938.

55 Courville, C. B., and Mason, V. R. The Heart in Acromegaly, *Arch. Int. Med.* **61**: 704 (May) 1938.

development This hypertrophy may be present in the absence of the usual causes of cardiac enlargement No constant histologic alteration is present in the myocardium which distinguishes the enlarged heart in acromegaly from other enlarged hearts The authors conclude that the heart failure is directly related to the acromegalic process

#### PERICARDITIS

*Acute Pericarditis*—Stewart and his associates<sup>56</sup> have made interesting observations on a young patient suffering from chronic pericardial effusion which appeared to be due to a primary lesion The patient was not acutely ill and attended school in the intervals between therapeutic pericardial taps It became apparent that slowly developing cardiac tamponade was responsible for the patient's symptoms, for removal of the fluid resulted in dramatic improvement It was found that as fluid accumulated in the pericardial cavity in sufficient quantity, the venous pressure rose, the cardiac output became markedly decreased both per minute and per beat, the heart rate increased and the circulation time became longer When the excess pericardial fluid was removed, these abnormal conditions tended to disappear

Electrocardiographic changes in pericarditis<sup>57</sup> have continued to receive considerable attention The comprehensive and critical report of Winternitz and Langendorf is especially noteworthy Seventy-six cases of pericarditis were minutely analyzed and grouped under the various etiologic factors involved The electrocardiographic alterations in pericarditis are considered as evolving in four general stages The characteristic changes in the first stage consist in elevation of the ST segment and the terminal portion of the QRS complex In the second stage the ST deviation disappears, and the T wave becomes lower in amplitude In the third stage the T wave becomes negative, while in the fourth stage there is restitution toward the normal Chest leads were not found to give much positive information, although the absence of change was helpful in the making of the differential diagnosis Bellet and McMillan, on the other hand, found that the use of leads IV, V and VI was an important aid and that additional information was sometimes obtained by placing the anterior electrode over the area of friction

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56 Stewart, H J , Crane, N F , and Detrick, J E Studies of the Circulation in Pericardial Effusion, *Am Heart J* **16** 189, 1938

57 Winternitz, M , and Langendorf, R Das Elektrokardiogramm der Perikarditis, *Acta med Scandinav* **94** 141 and 274, 1938 Bellet, S , and McMillan, T M Electrocardiographic Patterns in Acute Pericarditis Evolution, Causes and Diagnostic Significance of Patterns in Limb and Chest Leads, A Study of Fifty-Seven Cases, *Arch Int Med* **61** 381 (March) 1938

*Chronic Constrictive Pericarditis*—Burwell and Blalock<sup>58</sup> and Stewart and his associates<sup>59</sup> have made careful measurements of various alterations of the circulation in patients with constrictive pericarditis. These alterations include a decrease in cardiac output, in blood velocity and in blood pressure and an increase in venous pressure, in total blood volume and in the heart rate at rest. As a result of these changes the now familiar clinical picture is seen, characterized by dyspnea on exercise, weakness and marked venous congestion, with cough, ascites and edema.

#### THE HEART IN PREGNANCY

Fetal electrocardiography during pregnancy has been carried out successfully during the past few years. Bell<sup>60</sup> and Strassmann and Mussey<sup>61</sup> have recently reviewed the subject and have published electrocardiograms showing waves undoubtedly of fetal origin. The latter authors have described a simple method which proved successful in recording fetal electrocardiograms in 52 cases during the last seventy days of pregnancy. The chief points in their technic were:

- 1 The patient is placed flat on her back on a couch.
- 2 The skin and the electrodes are moistened with saturated saline solution.
- 3 The electrodes are placed on the upper arms and left thigh.
- 4 The electrodes then are fastened with bandages 4 inches wide which have been soaked in saturated saline solution.
- 5 The patient rests ten to fifteen minutes before the electrocardiogram is taken.
- 6 Tracings are taken with the usual leads (I, II and III).
- 7 The electrode is changed from left thigh to right thigh.
- 8 Tracings then are repeated with leads II and III (right arm—right thigh, left arm—right thigh, respectively).
- 9 Two feet of film should be taken for each tracing.
- 10 Outside disturbances from other electric apparatus should be guarded against.

The importance of obtaining graphic evidence regarding the viability of the fetus and the rate, rhythm and regularity of the cardiac action is emphasized.

Burwell<sup>62</sup> has found that the major alterations in the circulation of pregnant women include:

- (1) An increase in heart rate, (2) a fall in the diastolic blood pressure, (3) an increase in the cardiac output out of proportion to the increase in oxygen con-

58 Burwell, C. S., and Blalock, A. *Chronic Constrictive Pericarditis: Physiologic and Pathologic Considerations*, J. A. M. A. **110** 265 (Jan. 22) 1938.

59 Stewart, H. J., Heuer, G. J., Deitrick, J. E., Crane, N. F., Watson, R. F., and Wheeler, C. H. *Measurements of the Circulation in Constrictive Pericarditis Before and After Resection of the Pericardium*, J. Clin. Investigation **17** 581, 1938.

60 Bell, G. H. *The Human Foetal Electrocardiogram*, J. Obst. & Gynaec. Brit. Emp. **45** 802, 1938.

61 Strassmann, E. O., and Mussey, R. D. *Technic and Results of Routine Fetal Electrocardiography During Pregnancy*, Am. J. Obst. & Gynec. **36** 986, 1938.

62 Burwell, C. S. *The Placenta as a Modified Arteriovenous Fistula, Considered in Relation to the Circulatory Adjustments to Pregnancy*, Am. J. M. Sc. **195** 1, 1938.

sumption, (4) an elevated venous pressure in pelvis and legs, (5) a relatively high oxygen content in the blood leaving the uterus, (6) an increase in total blood volume, (7) a loud bruit over the placenta

Among the many factors in pregnancy which may influence the circulation, Buiwell has suggested that two are of particular importance, namely, the obstruction offered by the enlarging uterus to the return of blood from the legs and the large blood supply to the placenta. In regard to the latter, it is emphasized that changes similar to those observed in pregnant women are known to occur in patients with arteriovenous anastomosis. A consideration of the structure of the maternal vascular system in the placenta led to the conclusion that to some degree an arteriovenous leak exists.

#### MISCELLANEOUS

*The Circulation in Pernicious Anemia*—Stewart, Crane and Detrick<sup>63</sup> have reported their observations on the circulatory responses to decreased oxygen capacity of the blood of 5 patients with pernicious anemia. These observations were first made during the period of anemia and later, after successful treatment. In the anemic state it was found that the stroke volume and the minute volume, the heart rate and the oxygen consumption were in all cases elevated and that the arm to tongue circulation time was decreased. Changes in the reverse direction occurred as the state of the blood approached normal. The venous pressure and electrocardiograms showed no significant alterations during the anemic state. The work of the left ventricle was not increased during anemia, in fact, the work per beat was less. The authors concluded that during the anemic state of pernicious anemia the heart is called on to pump an increased amount of blood per minute and that this is accomplished in part by an increase in the heart rate and in part by the maintaining of a greater output per beat. The red blood cells, though fewer in number, move at an increased velocity and, as a consequence, are used more frequently in the oxygen-carrying capacity.

*Heart Failure and Acute Nephritis*—Although it has long been known that heart failure may appear as a complication of acute nephritis, it has remained a rather neglected subject. During the past year a number of articles have appeared which have drawn attention to various clinical aspects of this problem. Langendorf and Pick<sup>64</sup> have critically reviewed the literature on heart failure and nephritis and have presented

63 Stewart, H. J., Crane, N. F., and Detrick, J. E. Studies of the Circulation in Pernicious Anemia, *J. Clin. Investigation* **16** 431, 1938.

64 Langendorf, R., and Pick, A. Elektrokardiogramm bei akuter Nephritis, *Acta med. Scandinav.* **94** 1, 1938.

their own studies, giving particular emphasis to the electrocardiographic alterations. The majority of their patients showed uniform modifications of the electrocardiogram, with a tendency toward discordant changes in the T wave in leads I and III. The full abnormality, not reached in every case, shows an inverted T wave in lead I and a large, pointed T wave in lead III. The T wave in lead IV may become inverted (new terminology), but the R wave remains unaffected, which aids in distinguishing this pattern from that of infarction of the anterior wall of the left ventricle. Displacement of the ST segment, indicative of cardiac infarction or of pericarditis, is not seen. These electrocardiographic alterations are associated in appearance with the rise in blood pressure but not with the clinical signs of heart failure. For this and other reasons the authors concluded that the electrocardiographic modifications observed are due in part to mechanical factors and in part to ischemic or inflammatory changes in the myocardium.

Debre and his co-workers<sup>65</sup> and Rubin and Rapoport<sup>66</sup> have ably discussed the cardiac complications of acute nephritis of childhood. The nephritis may appear insidiously and commonly follows infections of the upper respiratory tract. Cardiac disorders and heart failure were found to be frequent accompanying complications and appeared to be dependent on the extent of the myocardial damage and the degree of hypertension. The manifestations of cardiac involvement embrace the usual signs and symptoms of heart failure. Treatment should include restriction of the intake of fluids, a high carbohydrate diet and the use of magnesium sulfate for the control of hypertension and hypertensive encephalopathy.

*Neurocnclulatory Asthema*—Dorst<sup>67</sup> has found that chronic hypoglycemia frequently occurs in asthenic, undernourished patients who present the familiar picture of the "effort syndrome." His suggestion that the hypoglycemia may be partly responsible for the lack of vigor finds some confirmation in the improvement in his patients which followed treatment with small doses of insulin.

Soley and Shock<sup>68</sup> are of the opinion that the symptoms of the effort syndrome can be explained on the basis of respiratory alkalosis resulting from hyperventilation. Experiments on patients have been reported in which the symptoms of the "effort syndrome" were repro-

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65 Debré, R., Marie, J., and Seringe, P. Le syndrome hypertensif dans les néphrites aiguës de l'enfance, *Ann de méd* **44** 313, 1938.

66 Rubin, M. I., and Rapoport, M. Cardiac Complications of Acute Hemorrhagic Nephritis, *Am J Dis Child* **55** 244 (Feb.) 1938.

67 Dorst, S. Chronic Hypoglycemia. Problem in Carbohydrate Metabolism, *Am J M Sc* **196** 688, 1938.

68 Soley, M. H., and Shock, N. W. The Etiology of Effort Syndrome, *Am J M Sc* **196** 840, 1938.

duced by voluntary overbreathing and relieved after the administration of carbon dioxide. They concluded that the term neuocirculatory asthenia should be discarded and "anxiety state with (or complicated by) the hyperventilation syndrome" substituted. The reviewers are of the opinion that in only certain patients with neuocirculatory asthenia are the symptoms due to hyperventilation and that other factors are frequently responsible for the symptoms.

*The Effect of Smoking on the Cardiovascular System*—Thienes and Butt,<sup>69</sup> after analyzing the many reports on the effect of tobacco on the cardiovascular system, concluded that most of the work was improperly controlled and the reasoning highly uncritical. Their own experiments were carefully planned and designed to test the effect of daily injections of toxic doses of nicotine into rats and rabbits. The duration of the experiment was usually between three and six months. They found that vascular degeneration was greater in the control animals than in animals chronically poisoned with nicotine.

Segal<sup>70</sup> and Graybiel, Starr and White<sup>71</sup> have studied the effect of smoking as evidenced in the electrocardiogram. It is shown that in susceptible persons, significant lowering or inversion of the T wave occurs during and for a short period after the inhalation of tobacco smoke. Some proof is offered that these alterations in the T wave are not due to coronary vasoconstriction but to the characteristic action of nicotine on the cardiac ganglions.

*Cardiac Trauma*—There have been a number of reports<sup>72</sup> on various aspects of trauma of the heart to which the interested reader may refer for details.

#### HEART FAILURE AND ITS TREATMENT

Only a few general topics are mentioned under this heading, for the reason that treatment in the various types of heart disease has already been discussed.

69 Thienes, C. H., and Butt, E. M. Chronic Circulatory Effects of Tobacco and Nicotine, *Am J M Sc* **195** 522, 1938.

70 Segal, H. L. Cigarette Smoking. I. As a Cause of Fatigue, II. Effect on the Electrocardiogram With and Without the Use of Filters, *Am J M Sc* **196** 851, 1938.

71 Graybiel, A., Starr, R. S., and White, P. D. Electrocardiographic Changes Following the Inhalation of Tobacco Smoke, *Am Heart J* **15** 89, 1938.

72 Moritz, A. R., and Atkins, J. P. Cardiac Contusion. An Experimental and Pathologic Study, *Arch Path* **25** 445 (April) 1938. Barber, H. Trauma of the Heart, *Brit M J* **1** 433, 1938. Kissane, R. W., and Koons, R. A. Management and Treatment of Myocardial Contusion, *Tr Am Therap Soc* **38** 61, 1938. Kissane, R. W., Fidler, R. S., and Koons, R. A. Electrocardiographic Changes Following External Chest Injury to Dogs, *Ann Int Med* **11** 907, 1938. Elkin, D. C. The Diagnosis and Treatment of Wounds of the Heart. A Review of Twenty-Two Cases, *J A M A* **111** 1750 (Nov 5) 1938.



Altschule<sup>73</sup> has written an excellent monograph on the pathologic physiology of congestive heart failure. What particularly distinguishes this report from many others is the critical attitude maintained throughout and the absence of any crusading zeal in the support of some favored theory of the pathogenesis of heart failure. The presentation is divided into two parts. The first part deals with an analysis of the physiologic measurements of cardiac decompensation and the second with the interpretation of the physiologic knowledge in explaining the meaning of the cardinal symptoms of congestive failure. This report is recommended to all those wishing to review the present status of the knowledge of congestive failure.

McMichael<sup>74</sup> has shown that in man the normal increase in cardiac output which takes place with a change from the erect to the supine position diminishes and may disappear as cardiac failure progresses. This disappearance of the postural change in cardiac output is due to the inability of the heart to respond to the postural rise of venous pressure. Proof of this was seen when the cardiac output was correlated with the venous pressure in various stages of heart failure. In the early stage of heart failure the cardiac output drops, but the venous pressure remains normal. As the failure increases, the venous pressure rises, and the cardiac output also rises. In the late stages of cardiac failure the output falls below normal, despite a progressive rise of the venous pressure. These findings suggest the interesting probability that the increase in venous pressure associated with heart failure, rather than being a passive phenomenon depending on diminution of the cardiac output, is in the nature of a compensating mechanism which maintains the output of the heart at a higher level. This interpretation would explain many puzzling facts of cardiac behavior in congestive failure.

The amount of investigation and the sharp differences of opinion in regard to the therapeutic action of digitalis suggest that this drug has just recently been released for clinical trial. Moe and Visscher<sup>75</sup> have pointed out that the various methods of biologic assay now in use all involve determinations of the toxic dose of digitalis, with the tacit assumption that the therapeutically useful properties will vary in direct proportion to the toxic ones. They believe there is much evidence that this premise is incorrect, and, accordingly, they have studied the activity

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73 Altschule, M. D. *The Pathologic Physiology of Chronic Cardiac Decompensation*, *Medicine* **17** 75, 1938.

74 McMichael, J. *The Output of the Heart in Congestive Failure*, *Quart. J. Med.* **7** 331, 1938.

75 Moe, G. K., and Visscher, M. B. *Studies of the Native Glucosides of Digitalis Lanata with Particular Reference to Their Effects upon Cardiac Efficiency and Their Toxicity*, *J. Pharmacol. & Exper. Therap.* **64** 65, 1938.

of the separate pure native glucosides of *Digitalis lanata* on the basis of their physiologically useful properties. They have determined for the dog the minimum doses producing increased cardiac efficiency and those causing irregularities in rhythm. It was found that the ratio of the dose causing increased cardiac efficiency to the dose producing irregularities differs greatly for the different glucosides. The importance of this method of study is emphasized.

Katz and his associates<sup>76</sup> have studied the effect of digitalis on the dog, and their results indicate that this drug has no direct influence on the contractile powers or mechanical efficiency of the cardiac muscle, either in the "physiologic" or in the failing heart. They found that the chief if not the sole site of action of therapeutic doses of digitalis is on the peripheral vessels, especially those of the liver. In the animals with low arterial blood pressure there was an additional indirect effect on the heart due to improvement of the coronary flow by virtue of its pressor effect on the blood pressure. Cattell and Gold,<sup>77</sup> on the other hand, have demonstrated that in the isolated papillary muscle from the cat, digitalis bodies have a direct effect in increasing systolic tension. This increase was found to be independent of any effects which might be mediated through other influences on the intact heart. They concluded that shortening of the muscle fiber (decrease in diastolic size) is not essential to the explanation of the action of digitalis in increasing the force of contraction of the failing mammalian heart.

Stewart and his associates,<sup>78</sup> on the basis of clinical studies, believe that although digitalis acts directly on the cardiac muscle, the effect on systolic tension is not the most important. They consider the decrease in cardiac size to be the most significant effect of the drug and that the change in cardiac output is largely a consequence of this. Thus, in a normal person digitalis decreases the cardiac output and the cardiac size, even though there is reason to believe that the extent and the force of ventricular contraction increase. In other words, the effect on size in making the pump too small is the predominate one and results in a decrease in output. It was found that in the patient with heart failure, digitalization usually causes a reduction in the size

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76 Katz, L. N., Rodbard, S., Friend, M., and Rottersman, W. The Effect of Digitalis on the Anesthetized Dog. I. Action on the Splanchnic Bed, *J. Pharmacol. & Exper. Therap.* **62** 1, 1938. Katz, L. N., and Mendlowitz, M. Heart Failure Analyzed in the Isolated Heart Circuit, *Am. J. Physiol.* **122** 262, 1938.

77 Cattell, M., and Gold, H. The Influence of Digitalis Glucosides on the Force of Contraction of Mammalian Cardiac Muscle, *J. Pharmacol. & Exper. Therap.* **62** 116, 1938.

78 Stewart, H. J., Detrick, J. E., Crane, N. F., and Wheeler, C. H. Action of Digitalis in Uncompensated Heart Disease, *Arch. Int. Med.* **62** 569 (Oct.) 1938.

of the heart but that the accompanying change in cardiac output depends largely on the initial size of the heart. In the patient with an enlarged heart and congestive failure the output increases, while in the patient with a normal-sized heart and slight symptoms the output may increase, decrease or remain the same. However, the work of the heart per beat was found to be increased by digitalis in all types of heart disease, whether failure was present or not and whether there was auricular fibrillation or normal rhythm. The main conclusion of this work has been supported by the results of Starr and his associates,<sup>79</sup> who found that regardless of whether the cardiac output is increased or decreased, digitalis stimulates the heart in every instance, i. e., the work of the heart per beat in proportion to its size increases. This indicates that digitalis not only may benefit patients in congestive failure with cardiac enlargement but also may benefit certain patients with heart disease but without appreciable heart failure.

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<sup>79</sup> Starr, I., Gamble, C. J., Margolies, A., Donald, J. S., Jr., Joseph, N., and Eagle, E. A Clinical Study of the Action of Ten Commonly Used Drugs on Cardiac Output, Work and Size. On Respiration, on Metabolic Rate and on the Electrocardiogram, *J. Clin. Investigation* 16:799, 1937.

## News and Comment

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**Graduate Fortnight of the New York Academy of Medicine**—The twelfth graduate fortnight of the New York Academy of Medicine will be held from Oct 23 to Nov 3, 1939. The purpose is to make a complete study and authoritative presentation of a subject of outstanding importance in the practice of medicine and surgery—the endocrine glands and their disorders. The following topics are listed: “Historical sketch of the development of endocrinology, physiology of anterior lobe of pituitary gland, hyper and hypopituitarism, pituitary diencephalic syndromes, physiology of the ovaries, physiology of testes and therapeutic application of male sex hormones, puberty, menstruation and menopause, pregnancy, therapeutic application of female sex hormones, physiology of the parathyroid, hypo and hyper-parathyroidism, the adrenal cortex, the Cushing syndrome, neoplasms of adrenal and their clinical relations, overfunction of the adrenal cortex, the adrenal medulla, adrenal insufficiency, relation of diabetes to endocrine system, relationship of endocrines to nervous system, the physiology and principle inter-relations of the thyroid, hyperthyroidism and hypothyroidism, surgical treatment of hyperthyroidism and other diseases of the thyroid gland.”

A carefully integrated program will be presented which will include clinics and clinical demonstrations at many of the hospitals in New York, evening addresses and appropriate exhibits. The evening sessions at the Academy of Medicine will be addressed by recognized authorities in their special fields, drawn from leading medical centers of the United States. The comprehensive exhibit will include books and roentgenograms, pathologic and research material and presentations of clinical and laboratory diagnostic and therapeutic methods. It is also planned to provide demonstrations of exhibits.

All members of the medical profession are eligible for registration. A complete program and registration blank may be secured by addressing Dr. Mahlon Ashford, The New York Academy of Medicine, 2 East 103rd Street, New York.

## Book Reviews

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**The Collapse Therapy of Pulmonary Tuberculosis** By John Alexander, M A, M D, F A C S, Professor of Surgery of the University of Michigan, Surgeon-in-Charge of the Division of Thoracic Surgery, Department of Surgery, University of Michigan Hospital With contributions by the following Max Pinner, M D, F A C P, Herman M Briggs Memorial Hospital, Ithaca, N Y, Principal Diagnostic Pathologist, District Tuberculosis Hospitals, New York State Department of Health, John Blair Barnwell, M D, Associate Professor of Internal Medicine, University of Michigan, Physician-in-Charge of the Tuberculosis Unit of the Department of Internal Medicine, University of Michigan Hospital, Kirby Smith Howlett Jr, M S, M D, Resident, Laurel Heights State Tuberculosis Sanatorium, Shelton, Conn Price, \$15 Pp 705, with 367 illustrations Springfield, Ill Charles C Thomas, Publisher, 1937

Strictly, the title of this book is a misnomer. The author, together with the contributors, not only has considered those procedures which involve collapse of the lung but has completely covered the field of surgical treatment of pulmonary tuberculosis. The operative procedures are considered in the following order: paralysis of the phrenic nerve, scalenectomy and scalenotomy, pneumothorax, intrapleural pneumonolysis, oleothorax, paralysis of intercostal nerves, extrapleural pneumonolysis, subperiosteal and subcostal pneumonolysis, thoracoplasty, surgical drainage of the pulmonary cavity and surgical treatment of tuberculous empyema and tuberculosis of the thoracic wall. Each of the procedures is considered in detail. The indications and contraindications, the surgical technique, the preoperative and the postoperative care and the complications are discussed carefully and at length. When multiple operations are necessary the order and time of their performance are carefully set out.

Excellent photographs and drawings are used liberally, and equally good roentgen reproductions are most helpful. In addition, there is a review of the entire subject of collapse therapy, and a description is given of its development to the present. Most helpful also is the excellent discussion of the physiologic principles of collapse therapy and the pathology of pulmonary collapse. The book may be read with great profit by any one interested in the treatment of pulmonary tuberculosis, be he surgeon or internist.

In spite of his enthusiasm for surgical treatment, the author tries to maintain a balanced point of view. He repeatedly warns against surgical intervention unless the proper indications are present. He calls attention to the good results obtained in cases of minimal involvement when well regulated treatment is given in a sanatorium, without surgical intervention. But when one reads that 96.7 per cent of the patients in residence in one of the sanatoriums from which much of the material is drawn have had some sort of collapse therapy, one wonders if all the warnings have been heeded. It is doubtless true that certain surgical measures do no harm in cases of minimal involvement even when they might have been avoided. But this is true only when the surgical treatment is carried out by thoroughly competent surgeons.

The author speaks of the inadvisability for a physician to attempt collapse therapy until he has had adequate surgical training. Might it not be in order to protest against the attempt by the surgeon to treat pulmonary tuberculosis until he has had sufficient medical training in the evolution of this disease? Arguments of this sort are bound to involve matters of personal opinion, and while it seems that the pendulum has swung just a little too far toward the surgical side, this fact should not militate against the excellence of this book as a treatise on the surgical management of pulmonary tuberculosis.

**The Construction of Vulcanite Applicators for Applying Radium to Lesions of the Buccal Cavity, Lips, Orbit and Antrum** By Desmond Greer Walker, M A, M Dent Sc, M B, B Ch, Dental Registrar at the Middlesex Hospital Price, 5s Pp 61, with 12 illustrations London Middlesex Hospital Press, by John Murray, 1938

This monograph does not pretend to do more than discuss the technic for the preparation of radium applicators to be used in and about the mouth. It is taken for granted that the application of a radium pack has been chosen as the method of treatment and that the actual dose to be used has been prescribed by the radio-therapist.

If one is tempted to criticize the author's methods as unduly elaborate, one need only reflect that the proper geometric arrangement and fixation of radium applicators is a prime factor on which success or failure in the cure of cancer may often rest. One cannot be too meticulous in this regard. The construction of accurate models also provides permanent records of original lesions which may prove invaluable.

The author rightfully stresses the great importance of spacing in the protection of normal structures and recommends the use of lead for further protection. It should be made clear that in cases in which the use of lead is indicated, a thickness of 0.5 cm or more is necessary to be really effective. In many cases the use of lead may be rendered entirely unnecessary by effective spacing.

The text is particularly well illustrated. It should be of interest to any one called on to treat cancer of the oropharynx.

**The Harvey Lectures Series 32** Delivered under the auspices of the Harvey Society of New York, 1937-1938, under the patronage of the New York Academy of Medicine. By various authors Price, \$4 Pp 275, with 79 charts and illustrations Baltimore Williams & Wilkins Company, 1938

All who are acquainted with previous *Harvey Lectures* will find no occasion for surprise in the statement that the present series meets the same high standard set up by its predecessors. Each lecture is the exposition of an original piece of work carried out by the lecturer and is accompanied by an adequate bibliography dealing with the subject under discussion. Here is a source of original information for all who may have an interest in the subjects presented. The titles and the names of the authors are as follows: "The Nature of the Visual Process," by Dr Selig Hecht, professor of biophysics, Columbia University, "The Pasteur-Meyerhof Reaction in Muscle Metabolism," by Dr Einar Lundsgaard, professor of physiology, Institute of Medical Physiology, University of Copenhagen, "The Functional Significance of the Lymphatic System," by Dr Cecil K. Drinker, professor of physiology, Harvard University, "Transfers of Water and Solutes in the Body," by Dr John P. Peters, professor of medicine, Yale University, "Studies on the Cortical Representation of Somatic Sensibility," by Dr Philip Bard, Johns Hopkins University, "The Isolation and Properties of Tobacco Mosaic and Other Virus Proteins," by Dr Wendell M. Stanley, associate member of the Rockefeller Institute for Medical Research, Princeton, N. J., "The Chemistry and Biology of Male Sex Hormones," by Dr F. C. Koch, professor of biochemistry, University of Chicago, "Experimental Hypertension Induced by Renal Ischemia," by Dr Harry Goldblatt, professor of experimental pathology, Western Reserve University.

**Bienengift als Heilmittel** By Robert Schwab Price, 2.40 marks Pp 48 Leipzig Georg Thieme, 1938

The recent use of the poison of the honey bee in the treatment of patients suffering from the various forms of arthritis or neuralgia and the reports of the striking benefit resulting from such treatment have stimulated an interest in this therapeutic measure. Previous publications on the subject have been disappointing.

because of the lack of sufficient detail in the description of cases and the absence of a critical analysis of the results obtained. One picks up the present monograph with the hope that an adequate appraisal of bee venom as a remedy has at last been made. One finds, however, that the author has devoted twenty-two of the thirty-five pages that are directly on the subject to a discussion of the history of the use of bee venom in medicine, a discussion of animal venoms in general, a recounting of the physiologic action of the venom and a consideration of the question of immunity to it. The second part, which consists of twelve pages, is devoted to treatment with the venom of the honey bee. Much of the material is concerned with the work of others. The author used a salve containing bee venom in a total of 160 cases that were listed as follows: "acute as well as primary and secondary polyarthritis, arthritis deformans, myalgia, acute and chronic muscular rheumatism and neuritis and neuralgia." He reports that the best results were obtained in cases of neuralgia, neuritis and myalgia.

The reader finishes the book with the conviction that a critical evaluation of honey bee venom as a therapeutic agent is still to be written.

**A Textbook of Hematology.** By William Wagner, M.D., Pathologist, St Michael's Hospital, Toronto, Canada, and Lecturer in Pathology, University of Toronto. Price, \$4.50. Pp. 395, with 29 tables and illustrations. Philadelphia: P. Blakiston's Son & Co., 1938.

The author has written this book with a dual purpose in mind: to present the subject of hematology to practicing physicians in a manner that is readable and also to present techniques and data to those primarily interested in the study of disease by laboratory methods.

The volume is engagingly written and well illustrated with good colored plates, photomicrographs and charts. At the end are a well chosen bibliography and a comprehensive index. The entire book is constructed along workmanlike lines and is handsomely printed.

That the practicing physician will find it useful is self evident. The various clinical implications of modern hematology are well expressed, and the importance of the proper use of recently developed methods for studying and classifying the various disorders of the blood are explained in an interesting way. The laboratory worker—especially the student or teacher—also will like it. Techniques, the fine points in differential diagnosis and classification of blood cells or blood dyscrasias and the terminology of the modern hematologist are all clearly described.

On the whole, therefore, this new manual on hematology is a useful adjunct to any medical library. The author is to be congratulated on having put together such a pleasing textbook.

**Immune-Blood Therapy of Tuberculosis.** By Joseph Hollos. Price, \$2. Pp. 197. New York: Privately Printed, 1938.

Blood from rabbits "immunized" with a bouillon culture of human and bovine tubercle bacilli is hemolyzed, deproteinized and diluted (1:100,000). This material's "faculty of dissociation is so considerable that it shows several ions."

The stock solution is diluted further in a truly homeopathic manner, and therapy is generally started with a few minims of dilution 9 (1:1,000,000,000). This dilution of "immune-blood" may be rubbed in, injected or drunk—miraculous results ensuing regardless of the mode of exhibition. The results are documented by an amazing series of case reports, remarkable chiefly for a lack of specific detail. The whole unscientific mess is preceded by an introduction in which the author details his "persecution" by medical groups, first in Europe, now in America. Wistfully and unsuccessfully he compares his lack of recognition to the treatment of Semmelweis by his contemporaries.<sup>1</sup>

## TREATMENT OF MASSIVE HEMORRHAGE DUE TO PEPTIC ULCER

JOHN S. LADUE, M.D.

MINNEAPOLIS

There is no general agreement among internists on the question of withholding or giving food to patients with bleeding peptic ulcer. Most clinicians advocate a period of fasting, the giving of fluids and transfusions when needed and rest. Allen and Benedict<sup>1</sup> reported 138 cases of massive hemorrhage with a mortality of 14.5 per cent. This did not, however, include gross hemorrhage of mild and moderate degree, the mortality of all patients treated for gross hemorrhage being less than 2 per cent. Goldman<sup>2</sup> noted 40 deaths in 349 cases of gross hemorrhage, a mortality of 11.5 per cent. Eggleston<sup>3</sup> treated 95 patients without a fatality. Hinton<sup>4</sup> reported 52 cases with a 20 per cent mortality. Westermann<sup>5</sup> 50 cases with a 20 per cent mortality. Hendon<sup>6</sup> 46 cases with a 19 per cent mortality and Mannheim<sup>7</sup> 101 cases with an 8.9 per cent mortality for patients submitted to surgical procedure and a 4.1 per cent mortality for medically treated patients.

Ross<sup>8</sup> reported 187 cases with 6.5 per cent mortality. Aitken<sup>9</sup> 255 cases with 11 per cent. Bulmer<sup>10</sup> 578 cases with 10.7 per cent.

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From the Medical Service of Long Island College Hospital, Brooklyn.

1. Allen, A. W. and Benedict, E. B. Acute Massive Hemorrhage from Duodenal Ulcer. *Ann Surg* **98**: 736, 1933.

2. Goldman, L. Gross Hemorrhage from Peptic Ulcer. Its Morbidity, Mortality and Treatment. *J. A. M. A.* **107**: 1537 (Nov. 7) 1936.

3. Eggleston, E. L. Critical Review of Five Hundred Cases of Gastric and Duodenal Ulcer. *J. A. M. A.* **75**: 1542 (Dec. 4) 1920.

4. Hinton, J. W. Hemorrhage in Peptic Ulcer. *Ann Surg* **101**: 856, 1935.

5. Westermann, J. J. Bleeding Gastric and Duodenal Ulcers. *Ann Surg* **101**: 1377, 1935.

6. Hendon, G. A. The Treatment of Hemorrhage Caused by Peptic Ulcer. *Am J Digest Dis & Nutrition* **2**: 255, 1935.

7. Mannheim, S. D. The Incidence and Prognosis of Hemorrhage as a Complication of Gastroduodenal Ulcer. *M. J. & Rec* **124**: 98, 1926.

8. Ross, K. The Treatment of Haemorrhage from Peptic Ulcers. *M. J. Australia* **1**: 168, 1930.

(For other articles on this subject see page 1017)



Babey<sup>11</sup> 82 cases with 4.8 per cent, Chiesman,<sup>12</sup> 191 cases with 25 per cent, Davies and Nevin<sup>13</sup> 391 cases with 21.0 per cent, Burger and Hartfall,<sup>14</sup> 137 cases with 22 per cent, Gordon-Taylor<sup>15</sup> 21 per cent mortality, Paterson<sup>16</sup> 100 cases with 4 per cent mortality, Hellier and Camb<sup>17</sup> 202 cases with 13 per cent, Cullinan and Price,<sup>18</sup> 105 cases with 18.1 per cent and Bolton, Conybeare and their co-workers,<sup>19</sup> 600 cases with 2.5 per cent. Lynch<sup>20</sup> reported on 31 medically treated patients with a mortality of 12.9 per cent and 21 surgically treated patients with a mortality of 42.8 per cent.

It is interesting to note that the mortality rates from Guv's Hospital, London, reported by three different investigators varied from 2.5 to 22 per cent. These rates pertained to patients treated in essentially the same manner but from different services. Hence the wide variation can best be explained by assuming that the criteria defining gastric hemorrhage differed from service to service.

In 1906 Lenhartz<sup>21</sup> discussed a new therapy for bleeding ulcers, it differed from that generally in use in that patients were fed eggs and milk immediately. He treated 146 patients, with a mortality of 2.14 per cent. This appears to be the first instance recorded in the literature in which patients with bleeding peptic ulcer were given feedings at once as a part of their treatment.

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9 Aitken, R. S. Treatment of Profuse Bleeding from the Stomach and Duodenum, *Lancet* **1** 839, 1934.

10 Bulmer, E. Mortality from Hematemesis. Supplementary Analysis, *Lancet* **2** 720, 1932.

11 Babey, A. M. The Incidence, Mortality and Treatment of Hemorrhage in Gastric, Duodenal and Anastomatic Ulcer. *Guv's Hosp Rep* **86** 129, 1936.

12 Chiesman, W. E. Mortality of Severe Hemorrhage from Peptic Ulcers, *Lancet* **2** 722, 1932.

13 Davies, L., and Nevin, R. Prognosis of Hematemesis. Statistical Review, *Brit M J* **2** 858, 1934.

14 Burger, G., and Hartfall, J. Hematemesis in Peptic Ulcer, *Guv's Hosp Rep* **84** 197, 1934.

15 Gordon-Taylor, G. Attitude of Surgery to Hematemesis. *Lancet* **2** 811, 1935.

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17 Hellier, F. F. and Camb, M. A. Etiology and Mortality Rate of Hematemesis, *Lancet* **2** 1271, 1934.

18 Cullinan, E. R., and Price, R. K. Hemorrhage Following Peptic Ulceration. *St Barth Hosp Rep* **184** 213, 1932.

19 Bolton, C., Conybeare, J. J., Pyrah, L. N., and Cooke, A. M. Discussion on the Prognosis of Peptic Ulcers, *Proc Roy Soc Med* **27** 225, 1934.

20 Lynch, R. An Analysis of Ulcer of the Stomach and Duodenum, *Canad M A J* **17** 677, 1927.

21 Lenhartz, H. Ueber die Behandlung des Magengeschwurs, *Mitt a d Hamb Staatskrankenanst* **6** 345, 1906.

From Copenhagen Meulengracht<sup>22</sup> reported a series of 251 cases of severe hematemesis and melena with a mortality of 1 per cent. These patients were given a full puréed diet together with alkalis, administration starting on the day after admission. They were fed five times a day such foods as meat balls, timbales, broiled chops, omelet, mashed potatoes, vegetables au gratin, vegetable purées, vegetable soups, creamed vegetables, steamed apricots, applesauce, gruel, rice and tapioca pudding. No restrictions were placed on appetite.

Beinstein,<sup>23</sup> at the Jewish Hospital, Brooklyn, treated 28 patients with hemorrhage due to peptic ulcer, using a modified Andresen diet, without a fatality.

Carlson<sup>24</sup> demonstrated that active peristalsis and secretion take place in an empty stomach. Andresen,<sup>25</sup> at the Long Island College Hospital, based his treatment on these well known physiologic facts, reasoning that a stomach partly filled with food which combines rapidly with any gastric secretion is preferable to an actively contracting stomach full of secretions, which are likely to digest the clots plugging the bleeding vessel or the injured vessel wall itself.

In view of the discussion aroused by the recent paper of Meulengracht, whose results in feeding patients with hemorrhage due to peptic ulcer have just been cited, an exposition of Andresen's work should be of wide interest.

All patients with hematemesis and melena due to peptic ulcer admitted to the Long Island College Hospital are fed immediately and repeatedly. This treatment has been employed for all ward patients and for a majority of the private patients admitted to Long Island College Hospital during the last eighteen years.

The treatment was devised by Andresen in 1916. He first gave gelatin mixtures to patients recovering from gastroenterostomy. The results in these cases were so favorable that the same mixture was given to patients with gastric hemorrhage.

For purposes of comparison, mortality rates for series of cases reported here and abroad are given in table 1.

#### TREATMENT AT LONG ISLAND COLLEGE HOSPITAL

In the therapy for bleeding ulcer carried out at Long Island College Hospital there are four objectives: (1) stoppage of bleeding by

22 Meulengracht, E. The Treatment of Hematemesis and Melena with Food, *Lancet* 2 1220, 1935.

23 Bernstein, B. M. Experimental and Clinical Study of Hematemesis Due to Ulcer, *M. Rec.* 144 178, 1936.

24 Carlson, A. J. The Control of Hunger in Health and Disease, Chicago, University of Chicago Press, 1916.

25 Andresen, A. F. R. The Treatment of Gastric Hemorrhage, *J. A. M. A.* 89 1397 (Oct. 22) 1927.

formation of clots at the site of the hemorrhage, (2) prevention of an increase in blood pressure (already low as a result of hemorrhage) so rapid as to dislodge these clots, (3) management of shock, with avoidance of too much stimulation, which often results in recurring hemorrhage, and (4) prevention of digestion, by gastric secretion, of the exposed wound in the blood vessel or of the clots filling the defect.

Rest is essential if any of these objectives is to be realized. The patients must have absolute rest in bed and must be constantly reassured, lest fear and its resultant restlessness upset the entire regimen. Patients are usually morphinized for twenty-four hours or longer if necessary, the interval depending on the course of illness.

TABLE 1—*Mortality Rates of Hemorrhage Due to Peptic Ulcer*

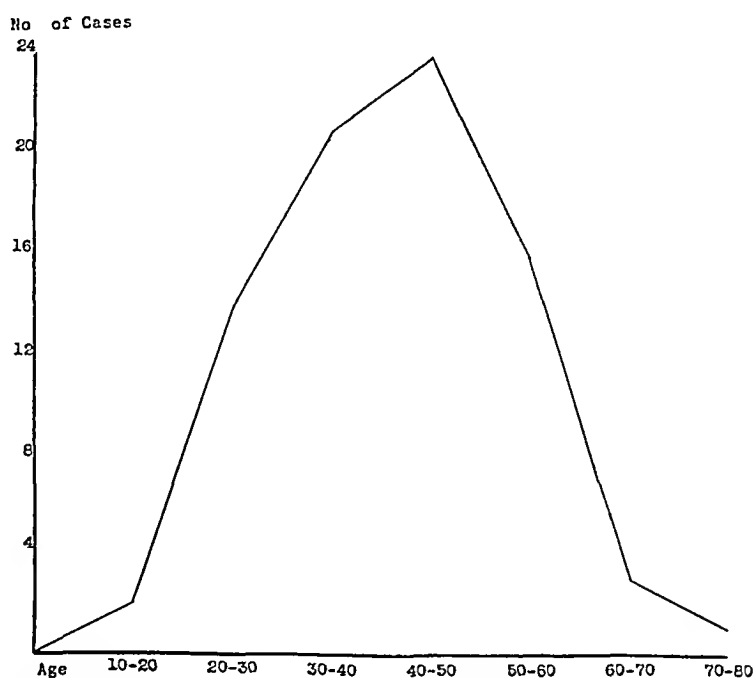
Author	Place	Number of Cases	Death Rate, Percentage
Treatment by Immediate and Repeated Feedings			
Lenhartz	Not stated	116	2.14
Meulengrucht	Copenhagen	2.1	1.0
Bernstein	Jewish Hospital, Brooklyn	28	0
Treatment by Period of Starvation			
Allen and Benedict	Massachusetts General Hospital	1.8	14.5
Goldman	San Francisco General Hospital	10	11.5
Westermann	St. Luke's Hospital, New York	70	20.0
Eggleston	Michigan	95	1.0
Manheim	Mount Sinai Hospital, New York	101	(total) 8.9
			(medical) 4.2
Hendon	Louisville, Ky.	46	10.0
Hinton	Bellerue Hospital, New York	72	20.0
Lynch	Montreal General Hospital	(medical) 31	12.9
		(surgical) 21	42.8
Ross	Australia	187	6.5
Altken	London Hospital	255	11.0
Bulmer	Birmingham, England	578	10.7
Babey	Guy's Hospital	82	1.8
Burger and Hartfall	Guy's Hospital	137	22.0
Bolton, Conybeare and others	Guy's Hospital	600	2.5
Chiesman	St. Thomas	191	25.0
Davies and Neyn	St. Thomas	391	21.0
Gordon Taylor	Middlesex	Not stated	21.0
Hellier and Camb	Leeds	202	13.0
Cullnan and Price	St. Bartholomew's Hospital	105	18.1
Paterson	London	100	4.0

The use of coagulants has been largely discontinued after a test period of several years, during which thromboplastin, horse serum, rabbit serum and human serum were found to have no noticeable effect.

Transfusions, intravenously administered fluids and clyses are rarely employed. Occasionally there are patients with obvious signs of a dangerously low blood volume, such as a feeble thready pulse, air hunger and markedly reduced blood pressure, they are given 150 to 200 cc. of blood by transfusion, which carries them out of shock. Intravenous injections of dextrose and clyses are withheld. Seven to ten days after hemorrhage, when there is no apparent danger of recurrent bleeding, one or more transfusions of 500 cc. of blood are of the greatest value and may materially shorten the period of convalescence.

Shock is combated with absolute rest in bed, heat, morphine and restoration of the blood volume, as just indicated. Stimulants are given rarely and with great caution, lest the patient's activity be increased enough to cause another hemorrhage. The surface of the body is kept warm with heaters, hot water bags and blankets. Nothing that might cause chilling, such as the use of ice bags over the epigastrium, is employed.

After hemorrhage the stomach is empty or is filled with blood, which is usually clotted. The blood, with its high protein content, acts as a powerful stimulant for the production of gastric juice, which rapidly digests the blood and may attack newly formed clots or even the injured wall of the blood vessel.



The age incidence in this series is roughly indicated by the graph. Seventy-five per cent of the patients were between 30 and 60 years of age. The largest single age group of those with hemorrhage, constituting 30 per cent of the cases, ranged from 40 to 50 years.

Emesis, melena and retching, always exhibited in some degree, indicate irritability of the gastrointestinal tract. The diet employed is designed to overcome this irritability and hypersecretion.

During the first two days after hemorrhage, 4 ounces (118 cc.) of a solution of gelatin half the strength used for making jelly, with added lactose and orange juice, is fed every one and one-half to two hours. Cereal, gruel, milk, lactose and cream mixtures may be added on the third day if there is no further sign of hemorrhage. A regular diet for patients with ulcer is instituted within a week to ten days after

hemorrhage. Thus a fluid intake of 1,920 cc is assured each day, with a minimum intake of 1,000 calories.

As the work of Carlson has shown, an empty stomach is never at rest, it appears desirable to keep the stomach as nearly at rest as possible by keeping it partly full. The diet just described is adequate in this respect, is soothing and combines rapidly with any gastric juice that may be present. Giving the gelatin mixture lessens the distressing thirst exhibited by the patients and supplies some nourishment. Roentgenograms are usually taken seven to ten days after bleeding ceases.

In table 2 are given the character and schedule of feedings. Table 3 describes the diet for patients with ulcer, and in table 4 is summarized the routine treatment for all patients with bleeding peptic ulcer.

#### STATISTICS FROM LONG ISLAND COLLEGE HOSPITAL

The patients with gastric hemorrhage admitted to the Long Island College Hospital from 1925 to 1936 inclusive and treated by Andresen's modified Lenhartz regimen were studied with respect to sex, incidence, previous history of ulcer, previous hemorrhage, type of ulcer, evidence of hemorrhage, gastric acidity and mortality. Only the 82 patients who appeared, according to all accepted criteria to have genuine ulcers were included. Each case was considered from the point of view of history, physical examination, roentgen examination and laboratory studies. In 17, or 20 per cent, of these cases roentgen study failed to reveal evidence of ulcer, but the gastrointestinal series were made from two to six weeks after all signs of bleeding had disappeared and the ulcers had had time to heal. In 7 of these cases there were no symptoms prior to hemorrhage, in the other 10 there were chronic gastric complaints. Duodenitis was ruled out in these cases by fluoroscopic studies.

All the patients had had bleeding severe enough to force them to seek hospitalization and all had bled shortly before entry. Red cell counts made on admission were less than 3,000,000, and hemoglobin levels were less than 60 per cent. Seventy-six patients exhibited symptoms and physical signs of severe hemorrhage on admission, i. e., restlessness, nausea, tenesmus, thirst, rapid shallow respiration, pallor, low blood pressure, syncope and collapse. The remaining 6 had these symptoms in a lesser degree at some time during their stay in the hospital.

Accepted criteria for hemorrhage from the gastrointestinal tract were hematemesis or melena or both. Of the 54 patients found to have duodenal ulcer, 2 had vomited blood, 13 had passed tarry stools and 39 had done both. The 11 patients with gastric ulcer both vomited blood and passed tarry stools. In the 17 cases in which the site of the ulcer was not definitely found, there were 4 instances of hematemesis, 1 of tarry stools and 12 of both. Thus, of the 82 patients 75 per cent had a

TABLE 2—*Long Island College Hospital Diet for Patients with Gastric Hemorrhage*

Character of Feedings		Ounces	Grams	Calories
Gelatin solution	Gelatin	1	30	128 0
	Lactose	3	90	360 0
	Juice of 1 orange			
	Water	32	1,000	47 8
Gruel mixture 1	Cereal gruel (oatmeal, barley or cornmeal)	16	500	338 5
	Milk	14	420	290 8
	Cream	4	120	458 9
	Lactose	3	90	360 0
Gruel mixture 2	Cereal gruel (same)	12	350	227 5
	Milk	32	1,000	692 0
	Cream	4	120	458 9
	Lactose	4	120	480 0
Schedule of Feedings		Ounces	Total Calories	
First and second day, feed every 1½ hours		Gelatin solution	4	947 2
Third day, feed every 1½ hours		Gelatin solution	4	1,365 4
		Gruel 1	5	
Fourth day, feed every 1½ hours		Gelatin solution	5	1,499 3
		Gruel 1	5	
Fifth and sixth day, feed every 1½ hours		Gelatin solution	6	3,600 0
		Gruel 2 *	6	
Seventh and eighth day, feed every 2 hours		Gelatin solution	6	3,600 0
		Gruel 2 *	6	
Ninth day and thereafter		Long Island College Hospital diet for patients with ulcer		

\* Add to gruel mixture at each feeding one of the following 3 oz cereal, 1 soft poached egg, custard or jello

TABLE 3—*Long Island College Hospital Diet for Patients with Ulcer*

Breakfast	Milk, 8 ounces, with cream if desired, cereal, 5 ounces, with milk or cream, egg, 1 soft boiled or poached, fruit juice or stewed fruit (end of meal)
Midmorning meal	Milk, 8 ounces, cream, ½ ounce, lactose, ½ ounce, with cocoa if desired, always with crackers, toast, bread or cake
Luncheon	Milk, 8 ounces, baked or mashed potato or plain spaghetti, egg, 1, soft boiled or poached, or cream cheese, bread and butter, 2 slices, pudding, custard, gelatin, ice cream or stewed fruit
Midafternoon meal	Same as midmorning meal
Supper	Same as breakfast or luncheon
Bedtime meal	Same as midmorning meal, repeat every 2½ hours during night if awake
Medication	Olive oil, ½ ounce, three times a day before meals, liquid petrolatum, ½ ounce, every night, water as desired

TABLE 4—*Routine Management of Patients with Gastric Hemorrhage*

I	Keep patient quiet by ordering enough morphine to prevent thirst, bromides and chloral hydrate, given by rectum, may also be administered
II	Order gastric hemorrhage diet (see table 2)
III	Type patient's blood, obtain donors, match blood
IV	Give no blood transfusions until after first week, unless indicated by air hunger, imperceptible pulse or markedly lowered blood pressure
V	Determine red cell count and hemoglobin content every 2 days, more often if hemorrhage persists
VI	Determine coagulation and bleeding time every 2 days and before and after transfusion
VII	Make no efforts at moving bowels for 3 days, on fourth night order warm oil enema (5 ounces to be retained), to be followed by small soapsuds enema on the next day if necessary, continue oil enema every night if needed
VIII	Test stools daily for occult blood until reactions are negative
IX	Avoid the following measures <ol style="list-style-type: none"> <li>1 Giving of ice, food or medicaments by mouth, except as indicated</li> <li>2 Sudden increase in blood volume by parenteral administration of fluids, except as noted in IV</li> <li>3 Raising blood pressure by use of epinephrine, ergot or blood stimulants, except in case of severe shock, when stimulants can be given coincidentally with transfusions</li> <li>4 Lowering of patient's body temperature and increase of shock by use of ice bags</li> </ol>
X	Keep patient warm

history of hematemesis and melena, 17 per cent of tarry stools alone and 7 per cent of hematemesis alone

Of these 82 patients, 58 or 70 per cent, were men and 24, or 30 per cent, were women. Fifty-four, or 66 per cent, had duodenal ulcer, 11, or 13 per cent, had gastric ulcer, and in 17, or 20 per cent, the site of bleeding was not found by roentgen examination. There was a previous history suggestive of ulcer in 72 cases, or 87 per cent, but in 10 cases, or 12 per cent, the hemorrhage was the first symptom noted by the patient. In 33 cases or 40 per cent, there was previous hemorrhage, but in 49, or 60 per cent, there was no history of bleeding. In 12, or 14 per cent, the patients had previously been admitted to Long Island College Hospital for hemorrhage.

Gastric analyses were done in 49 of the cases studied. In 27 or 56 per cent, an excessive amount of free hydrochloric acid was found, and the curve over the two hour period remained elevated. In 16, or 32 per cent, approximately normal curves were observed and in 5, or 10 per cent, the acidity was low. All the patients in this last group were at least 50 years old.

Transfusions were given to 17, or 20 per cent of the patients within one to ten days after admission and to 5 of the patients who died. Another 17 patients received blood before they were discharged but not until all signs of hemorrhage had disappeared and in no instance before the lapse of ten hospital days. The stools gave a positive benzidine reaction for from five to thirty days after entry.

All patients were examined for foci of infection, extraction of teeth and tonsillectomy being done when necessary. For the 10 patients readmitted for hemorrhage, foci were checked and corrected when necessary at the time of first admission.

One patient had had a posterior gastroenterostomy eighteen years prior to his admission for hemorrhage, and another had a similar procedure six months before his readmission for hemorrhage, the first operation having been performed three weeks after his initial hemorrhage. Two patients had a posterior gastroenterostomy after all signs of bleeding had disappeared.

None of the patients who died was operated on, in the 2 cases in which consent for autopsy was secured, the character and site of the lesions precluded any successful surgical procedure, in the opinion of the pathologist, internist and surgeon who were present at the autopsies.

Of the 82 patients, 8 died, 7 as a direct result of repeated hemorrhage. Three of these fatalities are not included in the mortality statistics because 1 patient died of pneumonia (contracted six weeks after entry) and 1 in the accident room ten minutes after admission, and 1 was not given feedings. Hence the mortality is 6.3 per cent.

One patient lived eight days after admission, the other 4, an average of twenty-six hours after the onset of their hemorrhage. The fatalities, except in the case of a 24 year old man who died in the accident room, occurred between the ages of 40 and 70 years.

Of the 5 cases in which death supervened, in only 1, case 3, was the Andresen therapy strictly followed. Patient 6 did not have an acute gastric hemorrhage, he had tarry stools for three weeks, and the diagnosis of bleeding ulcer was not definitely established, carcinoma of the stomach being the more probable lesion. Patient 5 was exsanguinated on admission and died twenty-four hours later. Patient 4 died after a massive transfusion (not advocated here), and patient 2 was given 500 cc of a 5 per cent solution of dextrose intravenously. Thus the mortality rate in cases in which the regimen outlined was strictly followed is only 13 per cent.

#### REPORT OF CASES IN WHICH DEATH OCCURRED

CASE 1—P A, a 55 year old Italian longshoreman, was admitted to the surgical ward with a history of hematemesis twenty-four hours prior to entrance. Two days later he vomited 200 to 300 cc of bright red blood. He was then placed on the regimen for gastric hemorrhage, but on the twelfth day in the hospital he again vomited bright red blood. He apparently responded well to treatment, and there were no further signs of bleeding.

On the twenty-second hospital day bronchopneumonia developed. Two days later evidence of cardiac decompensation appeared. The pneumonia failed to respond to treatment, and the patient died on the thirty-sixth day after his admission, without any further signs of hemorrhage. Permission for autopsy was refused.

This case is not included in the compilation of mortality statistics since the patient died of pneumonia after the gastric hemorrhage had been well controlled.

CASE 2—J C, a 72 year old Italian man, was admitted to the hospital with a history of hematemesis twenty-four hours prior to entry. On admission the patient was moribund and in shock, with cold, clammy skin, imperceptible pulse and shallow respirations. The blood pressure was 90 systolic and 60 diastolic. The red cell count was 4,950,000 and the hemoglobin content 112 per cent, the latter falling to 42 per cent a few hours later. Stimulants and sedatives were administered, and the patient was given 500 cc of a 5 per cent solution of dextrose. He continued to vomit coffee grounds material and passed several tarry stools. He died sixteen hours after admission, without having been given the usual treatment for hemorrhage.

Autopsy disclosed that the stomach was distended. The mucosa was coated with disorganized blood and mucus. No ulcer was observed in the stomach. The duodenum showed several small ulcers about 3 cm below the pylorus.

This patient was given 500 cc of a 5 per cent solution of dextrose intravenously, a measure contraindicated in the therapy described here.



CASE 3—J K, a 41 year old man, was admitted to the hospital with a history of passing two or three tarry stools a day for three days before entry. Physical examination gave essentially normal results. The blood pressure was 108 systolic and 70 diastolic. The red cell count was 2,000,000 and the hemoglobin content 44 per cent. The regimen for gastric hemorrhage was started, but eighteen hours later the patient vomited about 1,000 cc of dark red clotted blood. He was given 200 cc of blood by transfusion but died fourteen hours later.

At autopsy the stomach contained about 600 cc of thin reddish black blood, the rugae were prominent, and the mucosa was stained bright red. An ulcer, 1.5 cm in diameter, was observed at the pylorus at the line of transition between the duodenum and the gastric mucosa. The mucosal margin of the ulcer was soft and overhung the base of the ulcer, which was formed by dense fibrous tissue from a few millimeters to a centimeter thick. The gastroduodenal artery extended across the center of the base of the ulcer. Lateral erosion of its wall was noted, this admitted a probe 3 mm in diameter. The remainder of the duodenum was normal.

In this case autopsy revealed a pathologic condition not amenable to surgical treatment.

CASE 4—G C, a 48 year old Italian longshoreman, was admitted to the hospital with a history of vomiting a pint (473 cc) of bright red blood one hour prior to entry. Two years previously a series of roentgen examinations of the gastrointestinal tract failed to reveal any pathologic change.

Physical examination revealed cyanosis. The blood pressure was 70 systolic and 50 diastolic. The red cell count was 3,100,000 and the hemoglobin content 70 per cent. The Wassermann reaction was 4 plus. Hematemesis occurred twelve times during the patient's first twenty-four hours in the ward. A transfusion of 500 cc of blood was given, the patient died eight hours later. Permission for autopsy was refused.

In this case a massive transfusion was given, a procedure contraindicated if the tenets of therapy advocated by Andresen are to be followed strictly.

CASE 5—D L, a 41 year old Italian man, vomited a quart (946 cc) of bright red blood twenty-two hours before entry to the hospital and passed several tarry stools. Physical examination revealed that he was cadaverous, with a cold clammy skin. The blood pressure was 120 systolic and 80 diastolic. The red cell count was 850,000, the hemoglobin content was 10 per cent. A transfusion of 250 cc of blood was given, but twenty-four hours later the patient went into shock and failed to respond to treatment. Permission for autopsy was refused.

Since this patient was exsanguinated on admission and died within twenty-four hours, the data might have been excluded from the mortality statistics.

CASE 6—J K, a 52 year old man, entered the hospital with a history of passing one or two tarry stools a day for three weeks prior to entry. Physical examination gave essentially normal results. The blood pressure was 100 systolic and 80 diastolic. The red cell count was 4,430,000 and the hemoglobin content 74 per cent.

The patient was given the routine treatment but complained bitterly of gastric pain. On the fourth day he vomited about a pint of coffee grounds material. He continued to vomit two or three times a day for the next week, sometimes raising food just eaten and sometimes brownish material. On the eighth hospital day the patient vomited all feedings and went into shock. He died twelve hours later, despite treatment. Permission for autopsy was refused.

In this case the diagnosis of bleeding peptic ulcer was never firmly established, carcinoma being more likely.

CASE 7—B S, a 68 year old housewife, who had been discharged from the hospital one week previous to the present admission after recovery from gastric hemorrhage, was readmitted after she had begun to pass tarry stools. Physical examination revealed that she was pale, stuporous and moribund. The blood pressure was 124 systolic and 80 diastolic. The red cell count was 1,000,000 and the hemoglobin content 35 per cent. The patient was given 500 cc of blood by transfusion, but shortly afterward she went into shock, she died sixty hours after readmission. Consent for autopsy was refused.

This patient was not given the feedings for gastric hemorrhage. A transfusion of 500 cc was given one hour before death.

CASE 8—I V, a 24 year old Mexican man, was brought into the hospital by the ambulance surgeon with a history of having vomited copious quantities of bright red blood. Physical examination revealed that he was in extreme shock. He died ten minutes later, before any treatment could be given. Permission for autopsy was refused.

This patient died in the accident room before any form of treatment could be given.

#### COMMENT

All methods of treating gastric ulcer emphasize the need for absolute rest and the use of opiates when necessary. Aside from this general concurrence, treatment varies widely, some authorities insisting that fluids given parenterally and transfusions are essential, others that fluids of all sorts are contraindicated. Most clinicians prefer a period of fasting, while Lenhartz, Andresen and Meulengracht stated that they advocate feedings.

The rationale of feeding patients with bleeding ulcer has already been discussed. It is, however, pertinent to note again that an empty stomach contracts actively and produces gastric secretion. Since the purpose of any treatment is primarily the stopping of hemorrhage, it is reasonable to strive to keep the stomach as completely at rest as possible. Equally important is the inactivation of potent gastric secretions which may digest clots formed in the bleeding vessel or the vessel wall itself.

All these criteria seem to be met best by the diet outlined by Andresen, which is given in frequent small feedings and consists of a bland gelatin mixture capable of combining rapidly with the gastric juices.

The distressing thirst of which the patients complain is greatly lessened by the feedings, and no amount of reassurance is so effective in quieting their worry as the giving of nourishment so soon after hemorrhage. Early feedings are believed to be important in lessening the length of hospitalization, which averages twenty-seven and one-half days at Long Island College Hospital.

Fluids are not given intravenously and parenterally, the desirability of the procedures being far outweighed by the danger of increasing the blood pressure to a point high enough to dislodge clots already formed. When possible, transfusions are avoided early in the treatment for the same reason, but they are given in 200 to 300 cc portions when it is believed that the patient is dying for lack of blood. Occasionally one such transfusion will carry a patient past the danger point, but it is again emphasized that transfusions are reserved for the exsanguinated, moribund patient and are not given routinely.

Of the 7 patients who died directly as a result of continued bleeding, 5 received transfusions or fluids (in 3 cases in amounts not advised here). Seventeen patients were given small transfusions before the tenth hospital day. After all signs of hemorrhage have disappeared, blood is administered with great benefit and may shorten the period of hospitalization by several days.

When various mortality statistics are compared, variations of from 1 to 20 per cent are found, the rate being consistently higher whenever there was surgical intervention. Thus, at one hospital 5 of 7 patients subjected to operation died, at another all died. It is indeed rare that an acutely bleeding patient recovers after a surgical procedure. As the mortality of the operation itself is higher than the mortality to be expected from conservative treatment of bleeding ulcers, this form of therapy should be reserved for the unusual patient. The operation, once performed, affords no guarantee of freedom from recurrent hemorrhage, for Balfour<sup>26</sup> found that 13 per cent of all patients had recurrent bleeding after operation. Hinton, Westermann and Hurst<sup>27</sup> also observed recurrent hemorrhage after surgical procedures. Lynch reported on 21 patients surgically treated, with a mortality of 42.8 per cent, and on 31 medically treated, with a mortality of 12.9 per cent.

Taken alone, the mortality of 63 per cent at Long Island College Hospital is no brief for the treatment of bleeding ulcers by immediate and repeated feedings, but when considered with the 21 per cent mortality reported by Lenhartz, the 1 per cent mortality of Meulengracht and the 0 per cent mortality of Bernstein it becomes significant. It is

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<sup>26</sup> Balfour, cited by Hurst<sup>27c</sup>

<sup>27</sup> (a) Hinton<sup>4</sup> (b) Westermann<sup>5</sup> (c) Hurst, A. F. The Incidence, Mortality and Treatment of Hemorrhage in Gastric, Duodenal and Anastomatic Ulcer, *Guy's Hosp. Rep.* 86:135, 1936.

noted in table 1 that mortality rates vary from 1 to 25 per cent, for patients deprived of food, but only five investigators reported a mortality below 63 per cent

It may be concluded that a certain percentage of patients with bleeding ulcer will die, regardless of treatment, but the fundamentals of therapy must be met by aiding the physiologic processes of healing. This can best be done by putting the stomach as nearly at rest as possible, inactivating the gastric secretions and maintaining the general body nutrition. The modified Lenhartz regimen of Andresen meets all these criteria physiologically and will, it is hoped, find a deservedly wider use in the future.

#### SUMMARY

Eighty-two patients with hemorrhage due to ulcer were admitted to Long Island College Hospital from 1925 to 1936, 54, or 66 per cent, had duodenal ulcer, 11, or 13 per cent, gastric ulcer, and in 17, or 20 per cent, the site of hemorrhage was not found by roentgen study.

Treatment in all cases included rest in bed, administration of morphine and immediate and repeated feedings as outlined. Parenteral injection of fluids was withheld, and transfusions were given only as indicated.

Of the 79 patients for whom the mortality rate is computed, 5, or 63 per cent, died as a result of continued bleeding. Of patients who were given the exact form of treatment outlined, only 13 per cent died.

Autopsy in 2 cases revealed pathologic conditions not amenable to surgical intervention.

Dr. Andresen and Dr. D'Albora gave encouragement and criticism.  
Minneapolis General Hospital

# A CRITICAL EVALUATION OF GASTRIC ANTACIDS

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A gastric antacid is a chemical substance introduced into the stomach for the purpose of lowering the hydrogen ion concentration, or acidity, of the gastric contents. Such antacids are in common use in medical practice, mostly in the treatment of peptic ulcer, and in addition they are employed extensively in self medication by those who have recognized the efficacy of sodium bicarbonate in the relief of several types of gastric distress. Of the host of substances which are capable of neutralizing acid, only a few are adaptable to use as gastric antacids, and not more than a dozen have received general attention in therapeutic practice.

Unexpected difficulties are often encountered in the use of antacids to lower gastric acidity, because no antacid has yet been found which will simply neutralize acid without exhibiting additional pharmacologic action. These side actions usually have been objectionable rather than desirable. Under these circumstances it is not surprising that the full value of antacids has most frequently been unrealized and that their use has been somewhat discredited. A more complete understanding of the mechanisms by which the antacids act will perhaps help to dispel much of the disagreement and misunderstanding which apparently surround them at present.

The gastric antacids assume their greatest importance in the therapy of peptic ulcer, and their use has been most extensive in this field. As a convenient way of bringing out the physiologic and pharmacologic principles involved, they will be discussed in relation to this disease. It is not the purpose here to defend the use of antacids for peptic ulcer or to give the impression that all difficulties will be avoided by adherence to the conclusions reached, for each patient requires individual analysis and treatment. The fact remains, however, that antacids are used extensively today, and their use on a rational basis must be predicated on a complete knowledge of their limitations and their possibilities, both favorable and unfavorable. Rivers,<sup>1</sup> speaking of peptic ulcer,

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From the Department of Pharmacology, School of Medicine, Emory University.

1 Rivers, A B. Certain Factors Important in the Etiology and Treatment of Peptic Ulcer, J M A Alabama 6 166-177, 1936.

stated, "It is unfortunately true that much of what is known is forgotten or ignored when a plan of treatment for the cure of the disease must be formulated" This statement seems to be especially true with regard to the use of antacids Thus the development of a rationale for the use of the antacids and an evaluation on this basis of the various antacids now available should be worth while

Antacids are generally conceded to be used for three primary purposes in the treatment of peptic ulcer (1) to allay pain, (2) to relieve pylorospasm and (3) to avoid digestion and corrosion of a lesion by acid chyme The first and second of these objectives are usually accomplished by moderate doses if the antacids are effective at all Simple neutralization of the contents of the stomach at the time of distress is the means by which two objectives are accomplished The third objective has been the source of most of the trouble resulting when antacids are used In the first place, the symptomatic relief afforded by the accomplishment of the first two objectives has been deceptive, leading to the supposition that the third objective is automatically attained also However, the amount of antacid sufficient to relieve pain and pylorospasm is far short of the amount necessary to prevent acid digestion and corrosion of the lesion during the greater part of the time Perhaps it is unnecessary to neutralize the contents of the stomach completely in order to prevent the deleterious action of acid chyme, and it is beyond question that ulcers do heal even in the presence of a moderate amount of gastric acidity It is yet to be proved, however, that healing under these conditions is not further evidence of the remarkable ability of the physiologic economy to effect recovery even though under a handicap and that recovery would not be facilitated by the practical absence of free acid

#### SIPPY POWDERS

In 1915 Sippy<sup>2</sup> promulgated a plan of treatment of peptic ulcer based on the principle of continuous prevention of acid corrosion and digestion of the lesion by the use of a bland diet and a mixture of antacid powders The diet was chosen with the aim of minimizing (1) the chances of trauma, (2) secretory stimulation and (3) gastric emptying time The powders, consisting of 0.6 Gm each of sodium bicarbonate and magnesium oxide in powder 1 and 0.6 Gm of bismuth subcarbonate with 2 to 3 Gm of sodium bicarbonate in powder 2, were administered alternately every hour The success attained by this regimen is well known, yet several objectionable features arose in this treatment which caused much modification in the powders by various clinicians

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<sup>2</sup> Sippy, B. W. Gastric and Duodenal Ulcer. Medical Cure by an Efficient Removal of Gastric Juice Corrosion, *J. A. M. A.* **64** 1625-1630 (May 15) 1915

The first serious difficulty encountered was the frequent appearance of untoward symptoms, which are now recognized as resulting from the production of systemic alkalosis by absorbable antacids. The following outline of the literature will provide the salient points of the clinical history of the Sippy treatment as a background for the ensuing discussion.

Sippy noticed certain unfavorable symptoms in patients on his regimen, but it was not until 1923 that the first detailed description of the syndrome was published.<sup>3</sup> Symptoms usually begin by the fourth day but may not appear until weeks after treatment begins.<sup>1</sup> Nervousness, introspection, irritability, anorexia and distaste for milk usually appear first. If the condition becomes worse there are headache, nausea, vomiting, vertigo, pains in joints and muscles, dry skin, dry throat, slow respiration, apathy, tetany, prostration and coma, usually in the order given.<sup>4</sup> Several deaths have been attributed to alkalosis produced by this treatment.<sup>5</sup> The laboratory evidence appears even earlier than the subjective symptoms<sup>6</sup> and is, indeed, often the only evidence by which mild forms can be correctly diagnosed. There is a rise in the carbon dioxide-combining power of the plasma,<sup>7</sup> in the uric acid and the crea-

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3 Hardt, L. L., and Rivers, A. B. Toxic Manifestations Following the Alkaline Treatment of Peptic Ulcer, *Arch Int Med* **31** 171-180 (Feb.) 1923

4 (a) Hardt and Rivers<sup>3</sup> (b) Cope, C. L. Alkali Poisoning A Danger in the Treatment of Gastric Ulcer, *Brit M J* **2** 914-917, 1936 (c) Kruse, F. H. Complications of Peptic Ulcer and Their Treatment, *J A M A* **109** 868-874 (Sept 11) 1937

5 (a) Gatewood, L. C., in discussion on Block, L., and Serby, A. M. Use of Alkalis in the Treatment of Peptic Ulcer, *J A M A* **92** 134-139 (Jan 12) 1929 (b) Youmans, J. B., and Greene, I. W. Clinical Alkalosis in Gastric Disease, *J Michigan M Soc* **23** 160-163, 1924 (c) Venables, J. F. Seven Cases of Alkalosis Following Alkaline Treatment of Duodenal Ulcer, *Guy's Hosp Rep* **75** 152-157, 1925 (d) Cooke, A. M. Alkalosis Occurring in the Alkaline Treatment of Peptic Ulcers, *Quart J Med* **1** 527-541, 1932

6 (a) Gatewood, W. E., Gaebler, O. H., Muntwyler, E., and Myers, V. C. Alkalosis in Patients with Peptic Ulcer, *Arch Int Med* **42** 79-105 (July) 1928 (b) Jeghers, H., and Lerner, H. H. The Syndrome of Alkalosis Complicating the Treatment of Peptic Ulcer, *New England J Med* **214** 1236-1244, 1936

7 (a) Koehler, A. E. Acid-Base Equilibrium I Clinical Studies in Alkalosis, *Arch Int Med* **31** 590-605 (April) 1923 (b) Hardt and Rivers<sup>3</sup> (c) Kruse<sup>4c</sup> (d) Youmans and Greene<sup>5b</sup> (e) Cooke<sup>5d</sup> (f) Jeghers and Lerner<sup>6b</sup> (g) Grant, S. B. Tetany A Report of Cases with Acid-Base Disturbance, *Arch Int Med* **30** 355-361 (Sept.) 1922 (h) Oakley, W. Alkalosis Arising in Treatment of Peptic Ulcer, *Lancet* **2** 187-190, 1935 (i) Koehler, A. E. The Effect of Acid and Base Ingestion upon the Acid-Base Balance, *J Biol Chem* **72** 99-121, 1927 (j) Jordan, S. M. Calcium, Chloride and Carbon Dioxide Content of Venous Blood in Cases of Gastroduodenal Ulcer Treated with Alkalis, *J A M A* **87** 1906-1909 (Dec 4) 1926

8 Hardt and Rivers<sup>3</sup> Kruse<sup>4c</sup> Venables<sup>5c</sup> Cooke<sup>5d</sup> Oakley<sup>7h</sup>

tinine<sup>9</sup> content and the  $p_H$ <sup>10</sup> of the blood and in the nonprotein nitrogen<sup>11</sup>. A decrease occurs in the chloride content of the blood<sup>12</sup> in the sulfate clearance<sup>4c</sup> and in the excretion of phenolsulfonphthalein,<sup>13</sup> and the urine is increased in amount<sup>7h</sup> and in alkalinity<sup>14</sup>. Casts and albumin are often seen,<sup>15</sup> and the chloride content of the urine is low<sup>4b</sup>.

The cause of the syndrome was obscure until Hardt and Rivers proved that milk was not the responsible agent and attributed the causation to absorbable alkaline powders. Sippy powders,<sup>16</sup> sodium bicarbonate alone,<sup>17</sup> sodium and potassium citrates and acetates<sup>18</sup> all have been proved capable of causing the syndrome. Contributing factors are renal insufficiency,<sup>19</sup> pyloric obstruction, vomiting,<sup>20</sup> a diet low in salt,<sup>21</sup> hemorrhage, anemia and impaired hepatic function<sup>6b</sup>. Loss of chloride also is a factor if much gastric residuum is removed by lavage in cases of retention<sup>7a</sup>.

Reports of the incidence of alkalosis in cases of peptic ulcer vary widely, 8 per cent,<sup>22</sup> 10 per cent,<sup>4c</sup> 20 per cent<sup>23</sup> and 47 per cent<sup>6a</sup>.

9 Hardt and Rivers<sup>3</sup> Kruse<sup>4c</sup>

10 (a) Gatewood, Gaebler, Muntwyler and Myers<sup>6a</sup> (b) Koehler<sup>7i</sup> (c) Binger, C A L, Hastings, A B, and Neill, J M. Edema Associated with Moderate Bicarbonate Administration During Convalescence from Pneumonia, *Arch Int Med* **31** 145-150 (Jan) 1923 (d) Kast, L, Myers, V C, and Schmitz, H W. Clinical Conditions of Alkalosis, *J A M A* **82** 1858-1861 (June 7) 1924

11 Kruse<sup>4c</sup> Oakley<sup>7h</sup>

12 Gatewood, Gaebler, Muntwyler and Myers<sup>6a</sup> Kruse<sup>4c</sup> Jordan<sup>7j</sup>

13 Kruse<sup>4c</sup> Cooke<sup>5d</sup> Jeghers and Lerner<sup>6b</sup>

14 Cope<sup>4b</sup> Jeghers and Lerner<sup>6b</sup> Oakley<sup>7h</sup>

15 Footnote 4 Cooke<sup>5d</sup> Oakley<sup>7h</sup>

16 Gatewood, Gaebler, Muntwyler and Myers<sup>6a</sup> Hardt and Rivers<sup>3</sup> Cope<sup>4b</sup> Venables<sup>5c</sup> Grant<sup>7g</sup>

17 Koehler<sup>7a</sup> Oakley<sup>7h</sup> Kast, Myers and Schmitz<sup>10d</sup>

18 Cope<sup>4b</sup> Koehler<sup>7i</sup>

19 (a) Kruse<sup>4c</sup> (b) Venables<sup>5c</sup> (c) Jeghers and Lerner<sup>6b</sup> (d) Kast, Myers and Schmitz<sup>10d</sup> (e) Chace, A F. Medical Aspects of Peptic Ulcer with Special Reference to Diagnosis and Treatment, *Am J Digest Dis & Nutrition* **1** 866-870, 1935

20 Kruse<sup>4c</sup> Jeghers and Lerner<sup>6b</sup> Ellis, A W M. Disturbance of Acid-Base Equilibrium of the Blood to the Alkaline Side, *Quart J Med* **17** 405-423, 1924 McVicar, C S. A Discussion of the Clinical and Laboratory Findings in Certain Cases of Obstruction in the Upper Gastrointestinal Tract. The Role of Blood Chemistry in Diagnosis, Prognosis, and Treatment of This Condition, *Am J M Sc* **169** 224-235, 1925

21 Jeghers and Lerner<sup>6b</sup> Chace<sup>19e</sup>

22 Jordan, S M, and Kiefer, E D. Factors Influencing Prognosis in the Medical Treatment of Duodenal Ulcer, *Am J Surg* **15** 473-482, 1932

23 Eusterman, G B. Gastric and Duodenal Ulcers. Factors Essential to Their Successful Medical Management, *Wisconsin M J* **34** 473-477, 1935



having been recorded. This variation is easily accounted for by differences in the dosage and by failure to recognize many cases of alkalosis.<sup>24</sup> The time when the blood is sampled also may lead to variations of data among investigators, since a patient who does not receive powders during the night tends to return to normal by morning. It is probable that when Sippy's recommendations are followed and enough alkaline powders are given to control acidity at all times the incidence is in the higher brackets, while the lower figures obtain in current practice in which the dosage is insufficient to avoid acid corrosion much of the time. On the other hand, it has been pointed out repeatedly<sup>25</sup> that the onset of alkalosis is so insidious and so many of the symptoms are common to other diseases that in a large number of cases the condition, especially when mild, is not recognized. It is easy to overlook the symptoms in the early stages and the condition may supervene weeks or months after treatment is instituted, even though no change in the dose or the routine has occurred. Hurst<sup>26</sup> said:

In common with Ryle and Hardy, I have seen patients who were thought to be dying from uraemia, but were really suffering from severe alkalosis, and

I believe that more deaths must result from unrecognized poisoning with alkaline powders than from accidental poisoning with the barbiturates.

*Mechanism of Action*—The explanation of the manner in which the administration of Sippy powders results in systemic alkalosis brings in a number of factors which have not always been apparent. The same mechanism operates when any absorbable alkali is considered, and thus Sippy powders may be conveniently referred to and should be regarded as an example of a general class of antacids—the systemic or absorbable antacids.

It can be shown by calculating from the data of Freezing, Gibson and Mathews<sup>26</sup> that the average patient following the unmodified Sippy regimen receives in one day antacid powders sufficient to neutralize 5,000 cc of 0.36 per cent, or 3,600 cc of 0.5 per cent, hydrochloric acid. The strengths of the acid are significant because 0.36 per cent represents the concentration of acid in the stomach after secreted acid is mixed with other contents of the stomach, while 0.5 per cent is the strength approached by the acid as it is secreted, before it is mixed with other contents. However, it may be safely estimated that the stomach does not secrete more than 2,000 cc of gastric juice in twenty-four hours (1,500 cc is probably nearer the upper limit), and even if the

24 Koehler<sup>7a</sup>, Cope<sup>4b</sup>, Youmans and Greene<sup>5b</sup>, Jegheers and Lerner<sup>6b</sup>, Oakley<sup>7h</sup>.

25 Hurst, A. F. Diseases of the Alimentary Canal, Practitioner **137** 409-422, 1936.

26 Freezing, C. R. E., Gibson, C. S., and Mathews, E. A Contribution to the Study of Alkalis as Therapeutic Agents, Guy's Hosp. Rep. **78** 191-198, 1928.

entire 2,000 cc were 0.5 per cent hydrochloric acid the amount of alkali administered in the same period would greatly exceed that necessary to neutralize this acid. The excess would be sufficient to neutralize at least an additional 1,500 cc of 0.5 per cent acid. These relations are shown in chart 1.

Notwithstanding the foregoing facts, it must be remembered that Sippy and subsequent workers found by analysis of the gastric contents that the amounts of alkaline powders which they recommended were actually necessary to prevent the appearance of free acid. Wosika and Emery<sup>27</sup> recently investigated the effectiveness of the Sippy regimen in neutralizing the gastric juice, with a powder consisting of calcium carbonate and sodium bicarbonate. Taking samples of the gastric

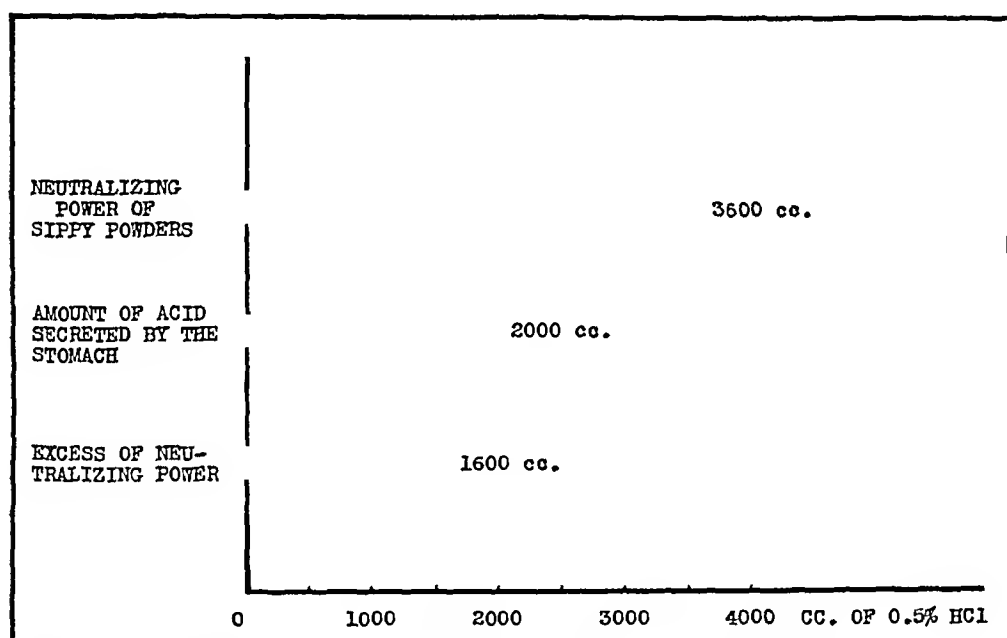


Chart 1—Total neutralizing power of the Sippy powders given in twenty-four hours (one each hour and four after 7 p. m.) compared with the amount of acid secreted by the stomach in the same time.

contents every half-hour throughout the day, they found that the condition was adequately controlled in only about 57 per cent of their cases, even though their interpretation of control was liberal. The total neutralizing power of all powders given each day in their series was equal to that of 30 Gm of sodium bicarbonate (unmodified Sippy powders are equivalent to 40 Gm of bicarbonate per day). In current practice the amounts of antacid given are usually materially less than this. How much more, then, would be the failure to control adequately

27 Wosika, P. H., and Emery, E. S. The Effectiveness of the Sippy Regimen in Neutralizing the Gastric Juice of Patients If the Amount of Alkali Is Not Varied, *Ann Int Med* 9:1070-1077, 1936.

the free acid<sup>1</sup> Why is an amount of alkaline powder calculated to be adequate insufficient in almost 50 per cent of cases? Reference to chart 2 will help to explain this

The interrelations of significance when absorbable antacid powders are ingested are indicated in chart 2. The average Sippy powder given by mouth provides each hour 27.5 milliequivalents of base. In addition, a significant amount of acid is neutralized by the milk taken during the hour, and also a small amount is neutralized by secreted saliva. When the antacid reaches the stomach it encounters the acid secreted there

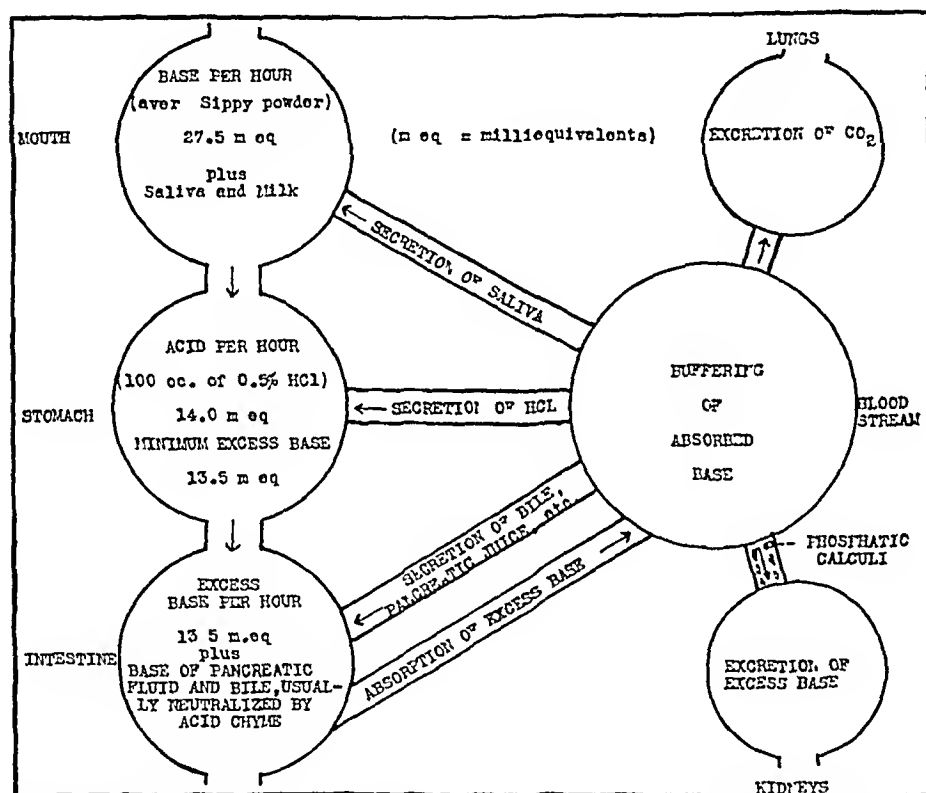


Chart 2—Interrelations affected when a systemic antacid is ingested

Ordinarily the amount of acid secreted in one hour approximates 50 cc of 0.5 per cent hydrochloric acid, yet under the conditions obtaining in cases of peptic ulcer it may be somewhat increased. Suppose then that in one hour the rate is doubled, to 100 cc of 0.5 per cent hydrochloric acid. This is 14 milliequivalents. In subsequent consideration the antacid value of the milk in the diet and that of saliva will be disregarded, even though it is a significant amount.

From these figures it is seen that the antacid powders provide an excess of base amounting to a minimum of 13.5 milliequivalents each hour. This is termed a *minimum* because the emptying of the stomach is facilitated by the neutralization as the gastric acid reacts with the

antacid Thus, *much of the antacid leaves the stomach before the hour has elapsed and is not available for the neutralization of acid subsequently secreted during that hour* It was estimated<sup>27</sup> that the amount of alkaline powder given by the Sippy regimen was 25 to 50 times as much as was used to neutralize acid, chiefly because of this factor

Another troublesome factor enters here The production of alkalinity in the stomach has been shown<sup>28</sup> to result in a "rebound" secretion of gastric acid which is greater than is encountered when the contents of the stomach are not made alkaline It is apparent, then, that while the alkaline powders directly cause their quick passage from the stomach they also cause an increased flow of acid into it after they leave it A vicious cycle is established—alkaline powders causing increased alkaline reaction in the stomach, alkaline reaction causing increased flow of gastric acid and increased amount of acid requiring larger amounts of antacid for neutralization Is it not possible that this factor may be the largest contributor to the hyperacidity in many cases of uncomplicated peptic ulcer?

The excess base passes into the stomach, where it is augmented by much alkaline fluid, mostly secreted by the pancreas and liver, which is normally partially neutralized by acid chyme This alkaline fluid is probably more alkaline in subjects with hyperacidity than in normal persons, since an increase in the alkalinity of the pancreatic secretion during increased secretion of acid has been noted<sup>29</sup> From these observations it is apparent that potential supply of absorbable base, in some instances large, constitutes the source of the systemic alkalosis, and it probably is superfluous to point out that the danger exists not only when the antacid is a single absorbable alkaline substance or a mixture of such substances but also when the powders are mixtures of absorbable and nonabsorbable substances

*Systemic Alkalosis*—As the blood takes up the excess base from the intestine the buffers in the blood are called into play to resist a change of  $p_H$  With this constant strain toward a more alkaline reaction, the sudden influx of unusually large amounts of base, especially when a pathologic condition of the kidneys delays the excretion of base or when chloride is lost either by vomiting or by repeated washing out of reten-

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28 Crohn, B. B. Effect of Antacid Medication on Gastric Secretion and Acidity, *Am J M Sc* **155** 801-819, 1918 Lockwood, B. C., and Chamberlin, H. G. The Effect of Alkalis on Gastric Secretion and Motility as Measured by Fractional Gastric Analysis, *Arch Int Med* **32** 74-81 (July) 1923 Boyd, T. E. Influence of Alkalies on the Secretion and Composition of Gastric Juice, *Am J Physiol* **71** 455-471, 1925

29 Neale, A. V., and Klumpp, T. G. Action of Histamine on the Pancreas, *J Clin Investigation* **9** 197-208 1930

tion fluid from the stomach,<sup>7a</sup> the buffers are often unable to cope with the situation, and a change of  $p_H$  results. The blood, it may be recalled, is unable to resist a change toward alkalinity as efficiently as it does a change toward acidity, for if the Henderson-Hasselbalch equation,<sup>30</sup> which relates the  $p_H$  of the blood to the relative amounts of the acid and the basic form of each buffer pair in the blood, is remembered, it may be shown that for the  $p_H$  of the blood to be normal, the  $p_K$  values of the buffers in the blood require that the ratio of buffer pairs be on the alkaline side of the point of maximum buffering efficiency in order to satisfy the equation. This means that as base is added the buffering efficiency of the blood is decreasing, while as acid is added the point of maximum buffering efficiency is approached, this point must be passed before an abnormal  $p_H$  can result. Since acidosis is seen so often clinically, it should not be surprising to find that the administration of antacids may easily cause alkalosis. In fact alkalosis can be produced simply by voluntary hyperventilation of the lungs.

*Argument*—It is true that most of the difficulties in the use of absorbable alkaline powders would be overcome if the dosage were sufficient to neutralize free acid without producing an alkaline reaction in the stomach. Unfortunately, it is difficult, if not impossible, to strike this balance.<sup>31</sup> Many modifications in the use of Sippy powders have been made with this objective in view, but physiologic conditions make success largely fortuitous and temporary. On the one hand is the Scylla of free acid and on the other the Charybdis of rebound secretion of acid, with no practical guiding points to aid the physician in steering a middle course to avoid these dangers. Analysis of the gastric contents may be made to determine the amount of antacid needed for neutralization at any given time, but gastric acidity varies from hour to hour, day to day and week to week, as disease or recovery progresses. There is no way, short of almost continuous analysis of the gastric contents, to be reasonably sure that the objective of the treatment is attained continuously.<sup>32</sup> Since constant analysis is impractical, there remain three courses which may be followed. 1. The dosage may be decreased so that

30 Hawk, P. B., and Bergeim, O. *Practical Physiological Chemistry*, ed. 9, Philadelphia, P. Blakiston's Son & Co., 1926, p. 426.

31 (a) Bloch, L., and Serby, A. M. Use of Alkalis in the Treatment of Peptic Ulcer, *J. A. M. A.* **92** 134-139 (Jan. 12) 1929. (b) Wosika, P. H., and Emery, E. S. The Value of a Mixture of Powdered Milk and Alkali for Neutralizing the Gastric Acidity of Patients with Peptic Ulcer, *Ann. Int. Med.* **9** 1078-1090, 1936. (c) Loevenhart, A. S., and Crandall, L. A. Calcium Carbonate in Treatment of Gastric Hyperacidity Syndrome and in Gastric and Duodenal Ulcer, *J. A. M. A.* **88** 1557-1559 (May 14) 1927.

32 Bloch and Serby<sup>31a</sup> Wosika and Emery<sup>31b</sup>

alkalinity is seldom produced in the stomach. This is done in much current practice, but the third objective of antacid treatment, which has been stated, is then seldom attained. 2 The dosage may be increased to insure that all acid, even the rebound secretion, is neutralized continuously. This results in systemic alkalosis in a high percentage of cases, as has been explained. Also, the constant high alkalinity of the contents of the stomach irritates the ulcer<sup>31c</sup> and is conducive to its chronicity,<sup>33</sup> and it may lead to impairment of the kidneys by the precipitation of sharp crystalline phosphates in the renal tubules when a constantly alkaline urine is produced.<sup>34</sup> 3 The dosage can be adjusted with the hope of obtaining a satisfactory middle course between 1 and 2. The condition is then one of a pendulum-like movement between alkalinity and the presence of free acid, as has been discussed, and the objective is practically impossible to accomplish.

In addition, a number of minor objections are specifically directed at sodium bicarbonate. The most serious of these is that when an ulcer is near perforation the release of carbon dioxide by chemical action of the antacid with gastric acid may lead to dangerous distention which may complete the perforation.<sup>35</sup> This objection would, of course, apply to any antacid capable of releasing carbon dioxide.

Thus, in choosing an antacid it is essential to keep in mind (1) the difference between a systemic and a nonsystemic antacid and (2) the possibility of rebound secretion of acid if the antacid is capable of producing an alkaline reaction in the stomach. Since systemic alkalization has not been shown to be of value in reducing gastric acidity and since the use of systemic antacids has been shown to be attended often by undesirable and deleterious sequelae, a nonsystemic antacid is rationally indicated as a first choice. Further, when a nonsystemic antacid is chosen, it should be one incapable of producing secondary secretion of acid or other such side effects. If systemic antacids are used, it is rational to give small doses frequently rather than large doses infrequently. This fact probably accounts in some part for the superiority of the results attained by a constant drip apparatus. Such an apparatus has proved efficacious in the use of nonsystemic antacids also.

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33 Kreis, L. Kausale Radikalheilung der Hyperazidität für konservative Behandlung, *Wien med Wchnschr* **4** 140-141, 1931.

34 (a) Hurst<sup>25</sup> (b) Loevenhart and Crandall<sup>31c</sup> (c) Rosenthal, E. Treatment of Gastric and Duodenal Ulcer, *Rev Gastroenterol* **3** 227-238, 1936 (d) Schrijver, J. The Sippy Treatment of Gastric Ulcer, *Nederl tijdschr v geneesk* **2** 1757-1772, 1925, abstracted, *J A M A* **85** 1848 (Dec 5) 1925.

35 Hurst, A. F. Recent Advances in the Treatment of Gastric Disease, *Brit M J* **2** 779-783, 1928.

## NONSYSTEMIC ANTACIDS

The objections to the use of absorbable alkaline substances as gastric antacids have led to a continued search for other substances better suited to this purpose. The progress, to date, consists of the introduction and use of chemical substances, either soluble or insoluble, which are practically unabsorbed from the alimentary canal and which are capable of lowering the free acidity to a desirable point.

*Magnesium Salts*—There is relatively little absorption of magnesium salts from the gastrointestinal tract, and the amount absorbed is insufficient to cause toxic effects. Magnesium oxide, carbonate, citrate, hydroxide and peroxide have antacid properties and might be expected to function well as gastric antacids if unmixed with systemic antacids. Unfortunately, however, the irritation and diarrhea which they frequently cause preclude their use except in limited amounts.<sup>36</sup> An equally serious objection to their use arises from the property of stimulating a rebound secretion of acid, a property in which magnesium oxide is surpassed by few drugs.<sup>37</sup> Magnesium phosphate and calcium phosphate, which will be discussed in the next paragraph, were perhaps the first neutral salts to be suggested as antacids to replace Sippy powders. Magnesium trisilicate is included under colloidal substances because of its special nature.

*Calcium Salts*—The use of tertiary calcium and magnesium phosphates to replace Sippy powders was suggested in 1923,<sup>37</sup> with reports of adequate control of acidity and no toxic symptoms or disturbance of the systemic acid-base balance. Their action as local antacids only was later confirmed,<sup>38</sup> and their superiority in many respects over absorbable alkaline powders was established. The reaction in the stomach cannot be carried beyond  $pH$  7 by these salts, and the constipating effect of the calcium may be balanced by the laxative effect of the magnesium. Some objections to their use may be made, however: (a) Calcium phosphate is rather ineffectual as an antacid,<sup>39</sup> (b) it is often difficult to adjust the dose of each component of a powder so that the laxative and the constipating effect are balanced and yet keep an optimum for the control of acidity, (c) the neutral reaction which

36 Bloch and Serby<sup>31a</sup> Loevenhart and Crandall<sup>31c</sup>

37 Greenwald, I. Gastric Antacids Which Cannot Act as Systemic Alkalis, *Proc Soc Exper Biol & Med* **20** 436-439, 1923. Kantor, J. L. Antacid Gastric Therapy, with Especial Reference to the Use of Neutral Antacids, *J A M A* **81** 816-818 (Sept 8) 1923.

38 Shattuck, H. F., Rohdenburg, E. L., and Booher, L. E. Antacids in the Medical Management of Peptic Ulcer, *J A M A* **82** 200-203 (Jan 19) 1924.

39 Crohn, B. B. The Clinical Use of Colloidal Aluminum Hydroxide as a Gastric Antacid, *J Lab & Clin Med* **14** 610-614, 1929.

the salts produce in the stomach stops digestion and removes the antiseptic quality of acid chyme<sup>40</sup>

Calcium carbonate was named as the "ideal" antacid in 1927<sup>31c</sup> This salt is insoluble in water, a potential alkali and incapable of eliciting a secondary secretion of acid It may produce a protective coating on an ulcer and have demulcent properties Undoubtedly superior in many respects in the field of gastric antacids, it is available in a number of official forms However, calcium carbonate is not without some properties which may be objectionable It releases carbon dioxide in the presence of free acid, which, as has been said, may be dangerous Fecoliths and chalk balls may result from its continued use in large amounts,<sup>41</sup> and constipation is sometimes severe<sup>61</sup>

A gel of calcium silicate also has been recommended as a gastric antacid and will be discussed under colloids

*Mucin*—Closely resembling gastric mucus, mucin was recommended as a gastric antacid in 1932,<sup>42</sup> however, even though it combines with more acid than most proteins, its antacid value is limited The beneficial effects come from its demulcent properties The preparations are comparatively expensive and have not proved as efficacious as desired<sup>43</sup>

*Hydrogen Peroxide*—The use of hydrogen peroxide as a depressant of gastric acidity has been shown to be unsatisfactory<sup>44</sup> It may cause hemorrhage from an ulcer, and in effective concentrations it produces too much discomfort In lesser concentrations it has unpredictable results

*Milk*—The antacid value of milk has perhaps been obscured by emphasis on its excellent food value unaccompanied by the secretagogic effect of meat broths and the like as the reason for its inclusion in the diet in cases of ulcer Being amphoteric, milk is capable of buffering about its own volume of average gastric contents (0.3 per cent hydrochloric acid) to  $p_H$  4, the point of no free acidity<sup>26</sup> The amphoteric nature of the milk in the Sippy diet helps to mitigate the alkalizing tendency of the excessive administration of alkaline powders On the other hand, the milk taken daily on the Sippy regimen would, itself, be able to buffer about 1,200 cc of normal gastric contents The fat

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40 (a) Crohn<sup>39</sup> (b) Guillermin, R. Hyperchlorhydrie et hydrate d' alumine colloidal, *Rev med de la Suisse Rom* **44** 243-246, 1924

41 Eusterman, G. B., and Balfour, D. C. *The Stomach and Duodenum*, Philadelphia, W. B. Saunders Company, 1935, p. 286

42 Fogelson, S. J. *The Treatment of Peptic Ulcer with Gastric Mucin Preliminary Report*, *J. A. M. A.* **96** 673-675 (Feb. 28) 1931, *Peptic Ulcer Its Treatment with Gastric Mucin*, *Am. J. Nursing* **32** 921-925, 1932

43 Chace<sup>19e</sup> Rivers, A. B. *Certain Newer Methods of Treating Peptic Ulcer*, *Am. J. Digest Dis. & Nutrition* **3** 698-704, 1936

44 Culmer, C. V., Atkinson, A. J., and Ivy, A. C. *Hydrogen Peroxide as a Depressant of Gastric Acidity*, *Am. J. Digest Dis. & Nutrition* **4** 219-223, 1937



content of a mixture of milk and cream would tend to decrease gastric secretion <sup>35</sup>

Milk to which is added small amounts of sodium bicarbonate,<sup>45</sup> lime water <sup>34a</sup> or a citrate <sup>30</sup> and alkalinized powdered milk <sup>31b</sup> have been used. Sodium citrate added to milk has an especial advantage in preventing large curds in the stomach by fixing the calcium of milk, which is essential to the curdling process.<sup>31</sup> Elimination of heavy curds reduces trauma to the ulcer. Indeed, milk, alone or with small amounts of antacids, is able to control mild peptic ulcer in many cases. Powdered milk, alkalinized with a Sippy powder containing calcium carbonate and sodium bicarbonate, is claimed <sup>46</sup> to be more effective than the same powder given in the usual manner on the Sippy regimen. The tablet form is an added advantage.

*Bismuth Compounds*—The bismuth compounds are useful adjuvants in antacid mixtures but are too inefficient as buffering agents to reduce acids satisfactorily unassisted. The subnitrate is without neutralizing power and may, even in moderate quantities, be toxic if certain bacteria are present in the intestine and cause the formation of nitrite from nitrate. Also, the oxycarbonate and the subgallate have practically no neutralizing power <sup>36</sup>. The slight amount of a bismuth salt which goes into solution exerts a mild astringent and antiseptic effect, and the protective and demulcent actions of these insoluble powders are their greatest virtues in the therapy of peptic ulcer. Objections to them may be made because (a) they color the stools (black) and thereby may obscure slight melena or may be a source of worry to the neurotic patient <sup>47</sup> and (b) they may be severely constipating and if used in large amounts for extended periods may lead to the deposit of concretions in the intestines <sup>48</sup>.

#### COLLOIDAL ANTACIDS

A great improvement in the armamentarium of the gastric antacids occurred with the introduction of unabsorbable colloidal substances which are capable of reducing gastric acidity to a desired level.

*Colloidal Aluminum Hydroxide*—This substance, a specially prepared, colloidal white powder, insoluble in water, tasteless, neutral and amphoteric, was presented at the French congress of medicine <sup>40b</sup> in 1922 and introduced into this country in 1929 <sup>39</sup>. Ordinary commercial powdered aluminum hydroxide does not exhibit the high buffering power

45 Winkelstein, A. One Hundred and Sixty-Nine Studies in Gastric Secretion During the Night, *Am J Digest Dis & Nutrition* **1** 778-782, 1935.

46 Wosika, P. H. The Control of Gastric Acidity in Peptic Ulcer by Alkalinized Powdered Whole Milk Tablets, *Am J Digest Dis & Nutrition* **3** 419-426, 1936.

47 Loevenhart and Crandall <sup>31c</sup> Hurst <sup>31</sup>.

48 Sollmann, T. A Manual of Pharmacology, ed 5, Philadelphia, W. B. Saunders Company, 1936, p 968.

of the colloidal form and is not as satisfactory.<sup>49</sup> The medicinal powder is used in doses of 1 or 2 Gm (15 to 30 grams), either dissolved in milk or water or compressed into tablets. One gram of the powder is capable of buffering 35 cc of tenth-normal hydrochloric acid to  $p_H$  4 in two hours.

The first liquid preparation of colloidal aluminum hydroxide to be reported in this country appeared in 1931,<sup>49</sup> a slightly astringent, gelatinous, white fluid hydrate, with a not unpleasant taste, usually flavored with peppermint. The dose is 4 to 16 cc (1 to 4 drachms) and each cubic centimeter is capable of buffering 15 to 16 cc of tenth-normal hydrochloric acid to  $p_H$  4 in four hours. On a basis of dry weight the aluminum hydroxide cream has the advantage of much greater buffering power, presumably because of the greater stability of the colloidal state when the preparation is not dried. Further advantages are (a) The diluted cream may be continuously dripped into the stomach,<sup>50</sup> which is specially advantageous for control of acidity in severe conditions and for the control of acidity at night, which is so often neglected.<sup>45</sup> (b) the gel is more easily administered, (c) it is more highly adsorbent.<sup>51</sup> Tablets of the powder, however, provide a convenient means of carrying the antacid on the person for relief of distress in emergencies.

Early reports<sup>52</sup> were so enthusiastic over the relief of hyperacidity afforded by colloidal aluminum hydroxide that a healthy skepticism of its merits ensued. Further investigations and experiences with it have now established the fact, fifteen years after its introduction, that it produces remarkable symptomatic relief from pain, nausea and vomiting, even in long-standing and severe conditions, and that relief is almost immediate.<sup>53</sup>

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49 Einsel, I. H., and Rowland, V. C. The Aluminum Hydroxide Treatment of Peptic Ulcer, Ohio State M. J. **28** 173-174, 1932.

50 (a) Dimmel, H. Ueber Neutralon, Wien klin. Wchnschr. **39** 1219-1220, 1926. (b) Woldman, E. E., and Rowland, V. C. A New Technique for the Continuous Control of Acidity in Peptic Ulcer by Aluminum Hydroxide Drip, Am. J. Digest. Dis. & Nutrition **2** 733-736, 1936.

51 Woldman, E. E., and Rowland, V. C. Continuous Acid Adsorption by Aluminum Hydroxide Drip in the Treatment of Peptic Ulcer, Rev. Gastroenterol. **3** 27-35, 1936.

52 (a) Guillermin.<sup>40b</sup> (b) Swalm, W. A. Aluminum Silicate (Kaolin) with Aluminum Hydroxide in Certain Intestinal Disorders, M. Rec. **140** 26-31 and 68-76, 1934.

53 (a) Crohn.<sup>39</sup> (b) Einsel and Rowland.<sup>49</sup> (c) Woldman and Rowland (footnotes 50 b and 51). (d) Heilpern, L. Alucol Therapy of Hyperacidity, Polska gaz. lek. **11** 349-352, 1932. (e) Einsel, I. H., Adams, W. L., and Myers, V. C. Aluminum Hydroxide in the Treatment of Peptic Ulcer, Am. J. Digest.

The percentage of poor results with colloidal aluminum hydroxide is 8.1 in the largest series (125 cases) for which figures are given<sup>53e</sup>. In another instance only 1 patient of 24 receiving this treatment showed poor results<sup>53g</sup>. Other reports show almost universal symptomatic relief. The unusual success obtained with this antacid is due, in part, to the ready cooperation of the patients, who find the results so satisfactory and the routine of treatment so acceptable that they are unwilling to use other antacids. Hospitalization is unnecessary in many cases in which it would ordinarily be indicated because of the quick recovery with the use of colloidal aluminum hydroxide. It is significant that no adverse reports on the use of this antacid have appeared.

The mechanism of action of colloidal aluminum hydroxide is multiple, and the importance of each part in producing the therapeutic result is difficult to evaluate. Its slight astringent and its demulcent property undoubtedly play a part. It is reported<sup>54</sup> that flaky curds presumably precipitated mucus, covering the folds of the gastric and the duodenal mucosa, are found at autopsy when animals are killed after receiving the preparation in large doses for a time. This protective action probably accounts for some of the good effects seen with therapeutic doses, since a preparation of aluminum hydroxide with low buffering power was not devoid of good effects<sup>55</sup>.

The colloidal forms, however, have considerable buffering power, and the buffering of free acid plays an important role in obtaining the more satisfactory results seen when they are used<sup>56</sup>. The physico-chemical properties of the colloid cause an adsorption of hydrochloric acid, which is characterized by an immediate rapid decrease in the functional acidity of the gastric juice, with a more gradual reduction continuing. The  $p_H$  cannot go beyond neutrality, and usually the increase is to approximately  $p_H$  4. Thus digestion may not be entirely stopped and a slight acidity, not sufficient to cause acid corrosion, exerts some antiseptic influence. Some reaction between the aluminum hydroxide and the hydrochloric acid takes place, with formation of aluminum chloride. In an alkaline intestine aluminum hydroxide is reprecipitated and the chloride reabsorbed. It is unlikely that the hydrochloric acid adsorbed by the colloid is excreted in the feces to any great extent, as Kreis stated<sup>53</sup> otherwise the mineral constituents of the blood would probably be disturbed. That the latter occurs has been disproved<sup>57</sup>.

The colloid probably exerts also an adsorptive action on toxins (histamine and the like in intestinal putrefaction), on gases and on

Dis & Nutrition **1** 513-516, 1934. (f) Adams, W. L., Ensels, I. H., and Myers, V. C. Aluminum Hydroxide as an Antacid in Peptic Ulcer, *ibid* **3** 112-120, 1936. (g) Jones, C. Colloidal Aluminum Hydroxide in the Treatment of Peptic Ulcer, *ibid* **4** 99-102, 1937.

54 Ivy, A. C., Terry, T., Fauley, G. B., and Bradley, W. B. The Effect of Administration of Aluminum Preparations on the Secretory Activity and Gastric Acidity of the Normal Stomach, *Am J Digest Dis & Nutrition* **3** 879-883, 1937.

bacteria, removing them from the ulcerated areas and from the intestine. This is strongly indicated by the particularly good results obtained in the treatment of intestinal disturbances, probably by the strong adsorptive power of colloidal aluminum hydroxide <sup>55</sup>

Concerning the mechanism of action of this antacid, it is highly significant that evidence is at hand to indicate that it combats three major factors in the causation of peptic ulcer, namely (a) trauma, by its protective and demulcent properties, (b) acid corrosion, by its antacid effect, (c) infection, by its adsorptive action on toxins and bacteria.

Toxic local effects which might be anticipated, since colloidal aluminum hydroxide is used as a protein precipitant, have been proved absent <sup>56</sup>. Systemic poisoning by aluminum and disturbance of the acid-base equilibrium also have been ruled out <sup>57</sup>. Further, the alkaline reaction of the intestine peptizes the aluminum hydroxide to a more stable gel with the absorption of more water, so that intestinal concretions are unlikely <sup>52b</sup>. Concretions have never been reported as a complication when aluminum hydroxide was used.

Direct evidence of the therapeutic value of colloidal aluminum hydroxide, in addition to the symptomatic relief already mentioned, is the rapid disappearance of the ulcer, as shown by fluoroscopic or roentgen examination, in an average of thirty days after its administration is begun <sup>53g</sup>. Recurrence of symptoms and relapses are relatively less frequent, but it must be remembered that there is no evidence that this or any other antacid affects the tendency to recurrence in patients with the ulcerative diathesis if care and discretion in the diet and habits are abandoned.

On the basis of its merits and freedom from the undesirable qualities of most antacids, it seems justified to repeat the statement, "it appears that colloidal aluminum hydroxide is the most satisfactory antacid thus far employed," <sup>53f</sup> and to add that slight constipation, which is easily controlled, is the only objection to the use of colloidal aluminum hydroxide which has been mentioned. The constipation usually occurs only with large doses. Five or six preparations are now on the market, and the cost of medication is less than when Sippy powders are used.

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55 Swalm <sup>52b</sup> Fradkin, W. Z. The Control of Rectal Bleeding in the Convalescent Ulcerative Colitis Patient, *J. Lab. & Clin. Med.* **22** 896-899, 1937.

56 Adams, Einsel and Myers <sup>53f</sup> Ivy, Terry, Fauley and Bradley <sup>54</sup> Beazell, J. M., Schmidt, C. R., and Ivy, A. C. The Effect of Aluminum Hydroxide Cream on Absorption from the Gastro-Intestinal Tract, *Am. J. Digest. Dis.* **5** 164-165, 1938.

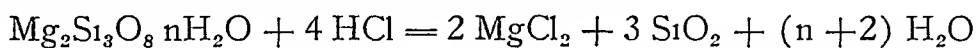
57 Adams, Einsel and Myers <sup>53f</sup> Ivy, Terry, Fauley and Bradley <sup>54</sup>

*Substances Used Personally to Lower Gastric Hyperacidity, with Some of the Data Useful in Rationally Choosing Among Them*

Substance	Soluble in Water of Gas	Adsorptive Power			Acid Neutralizing Power			Antacid Action		"Rebound" Secretion of Acid	Effect on Urine		Action on Bowels		Local Protective Action	Formation of Concrete Tonic Effects	Production of Toxic Effects
		High	Low	Absent	High	Medium	Low	Systemic	Local Only		Alkalinizes	Acidifies	Constipating	Laxative			
Aluminum hydroxide, colloidal		+			+			+					+	+			
Aluminum silicate																	
Bismuth subcarbonate U S P	+													+	+		
Bismuth subgallate U S P													+	+	+		
Bismuth subnitrate U S P													+	+	+		
Calcium carbonate, precipitated, U S P	+					+			+	+		+	+				+
Calcium hydroxide, solution U S P	+					+											
Calcium phosphate, precipitated, N I						+			+								
Hydrogen peroxide, solution U S P	+												+				+
Magnesium carbonate U S P									+					+	+	+	+
Magnesium magnesia U S P	+								+	+			+	+	+	+	+
Magnesium oxide heavy U S P									+	+			+	+	+	+	+
Magnesium peroxide	+								+	+			+	+	+	+	+
Magnesium phosphate tribasic									+								
Magnesium trisilicate, synthetic		+							+								
Milk (whole, sweet)																	
Potassium acetate U S P	+								+			+	+	+	+	+	+
Potassium bicarbonate U S P	+								+	+		+	+	+	+	+	+
Potassium citrate U S P	+								+	+		+	+	+	+	+	+
Sodium acetate U S P	+								+	+		+	+	+	+	+	+
Sodium bicarbonate U S P	+								+	+		+	+	+	+	+	+
Sodium citrate U S P	+								+	+		+	+	+	+	+	+
Sodium hydroxide (dilute solution)	+								+	+		+	+	+	+	+	+
Mineral waters	+						+					+	+	+	+	+	+

*Other Colloidal Substances*—Colloidal barium sulfate,<sup>58</sup> bismuth silicate<sup>59</sup> and calcium silicate<sup>60</sup> also have been suggested for use as gastric antacids. In general, they have not received enough attention to allow adequate judgment of their value.

*Magnesium Trisilicate*—Recently a synthetic hydrated trisilicate of magnesium<sup>61</sup> with adsorbent properties far superior to those of natural silicates has been introduced, and because of its unusual nature, it deserves more attention. It is a white, tasteless, insoluble powder, which reacts slowly with hydrochloric acid. One gram reacts with 155 cc of tenth-normal hydrochloric acid in four hours, the neutralization occurring rapidly at first and becoming slower as the reaction proceeds. Magnesium trisilicate is stated to react with hydrochloric acid in the stomach according to the following equation:



The silicon dioxide produced by this reaction is a hydrated gel without antacid properties, but it enters the duodenum and exerts a high adsorptive effect on toxins, bacteria and the like. The gel is thought to be a factor in producing a slower, more prolonged neutralization of acid, because it retards the diffusion of acid. Although its antipeptic, antacid and antitoxic properties seem to have been well studied,<sup>61</sup> the possibility of its producing a secondary acid rebound has not been ruled out yet, nor are studies of its toxicity complete and confirmed. In the single report of its use made since its introduction in 1936,<sup>62</sup> the results were said to be good.

#### SUMMARY

The various antacids which are used in the treatment of gastric hyperacidity and peptic ulcer are discussed from a pharmacologic point of view and much of the data which are of value in making a choice among them tabulated. The advantages and disadvantages of each are considered, and their pharmacologic actions, as shown by researches and clinical experiences, are used as a basis for evaluating the best antacids available at the present time.

58 Finkelstein, J. Colloidal Barium Sulfate in Hyperchlorhydric Gastritis, *Strasbourg méd* **96** 429-432 and 465-473, 1936.

59 Bonanno, A. M. Bismoterran (Bismuth Silicate Preparation) Therapy, *Minerva med* **1** 812-814, 1934.

60 Becher, E. Beobachtungen über Gastro-Sil, ein neues Mittel zur Behandlung der Hyperazidität, *Med Klin* **29** 20-21, 1933. Frisch, J. Beitrag zur Therapie der aciden Magenerkrankungen, *Wien med Wchnschr* **84** 1404-1406, 1934.

61 Mutch, N. The Silicates of Magnesium, *Brit M J* **1** 143-148, 205-208 and 254-257, 1936.

62 Mann, W. N. Experiments on the Neutralization of HCl by Magnesium Trisilicate, *Guy's Hosp Rep* **87** 151-157, 1937.

# CHANGES IN THE ACID-BASE BALANCE DURING ALKALI TREATMENT FOR PEPTIC ULCER

A CLINICAL ANALYSIS OF ALKALOSIS IN TWENTY-EIGHT PATIENTS

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CHICAGO

This paper presents biochemical and clinical studies on patients receiving alkali therapy for peptic ulcer, as well as an analysis of the clinical records of 28 patients in whom alkalosis developed during treatment for ulcer

Sippy<sup>1</sup> introduced the practice of using large daily doses of alkali powders for the treatment of peptic ulcer in 1915. He observed toxic symptoms in some of his patients (Gatewood and associates<sup>2</sup>). In 1923 Hardt and Rivers<sup>3</sup> published the first detailed account of alkali intoxication arising during the course of the Sippy treatment. They named the condition "alkalosis." Since that time cases of alkalosis have been reported with increasing frequency, so that the condition is now recognized as an important complication of the treatment of peptic ulcer (Hurst and Stewart<sup>4</sup>, Jordan and Kiefer<sup>5</sup>, Cooke<sup>6</sup>, Berger and Binger<sup>7</sup>, Oakley,<sup>8</sup> and others). In the majority of patients who receive the Sippy type of treatment symptoms of alkalosis do not, however, develop

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From the Department of Medicine, University of Chicago

1 Sippy, B. W. Gastric and Duodenal Ulcer. Medical Cure by an Efficient Removal of Gastric Juice Corrosion, *J. A. M. A.* **64** 1625 (May 15) 1915

2 Gatewood, W. E., Gaebler, O. H., Muntwyler, E., and Myers, V. C. Alkalosis in Patients with Peptic Ulcer, *Arch. Int. Med.* **42** 79 (July) 1928

3 Hardt, L. J., and Rivers, A. B. Toxic Manifestations Following the Alkaline Treatment of Peptic Ulcer, *Arch. Int. Med.* **31** 171 (Feb.) 1923

4 Hurst, A. F., and Stewart, M. J. Gastric and Duodenal Ulcer, London, Oxford University Press, 1929, p. 399

5 Jordan, S. M., and Kiefer, E. D. Factors Influencing Prognosis in the Medical Treatment of Duodenal Ulcer, *Am. J. Surg.* **15** 472 (March) 1932

6 Cooke, A. M. Alkalosis Occurring in the Alkaline Treatment of Peptic Ulcers, *Quart. J. Med.* **1** 527 (Oct.) 1932

7 Berger, E. H., and Binger, M. W. The Status of the Kidneys in Alkalosis, *J. A. M. A.* **104** 1383 (April 20) 1935

8 Oakley, W. Alkalosis Arising in Treatment of Peptic Ulcer, *Lancet* **2** 187 (July 27) 1935

Several theories have been proposed to account for the intolerance to alkalis occasionally encountered in certain persons. It was early recognized that in patients with renal disease alkalis are poorly tolerated, and alkalosis develops readily (Hardt and Rivers<sup>3</sup>). This observation has been confirmed by many investigators. High grade pyloric obstruction causing the loss of large amounts of gastric juice has been recognized as a cause of alkalosis by several observers (Brown and co-workers<sup>9</sup>, Gatewood and co-workers<sup>2</sup>, Huist and Stewart<sup>4</sup>, Oakley<sup>8</sup>, Jeghers and Lerner<sup>10</sup> and others). In fact, the loss of hydrochloric acid in pyloric obstruction may cause alkalosis when no alkalis have been administered (Grant<sup>11</sup>, Brown and co-workers<sup>9</sup>, Houghton and co-workers<sup>12</sup>, McArthur and Payne<sup>13</sup>, Pfeiffer<sup>14</sup>, Butler<sup>15</sup> and others). This has been shown experimentally also, by MacCallum and co-workers<sup>16</sup>. Hemorrhage was recognized as a contributory cause of alkalosis by Jordan and Kiefer<sup>5</sup>, Beigel and Binger<sup>7</sup>, Jeghers and Lerner<sup>10</sup> and others. Hepatic disease may be an etiologic factor according to Eusterman and Balfour<sup>17</sup>. Berger and Binger<sup>7</sup> expressed concurrence in this view. Kim<sup>18</sup> and MacNider<sup>19</sup> have shown experimentally that the

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9 Brown, G. E., Eusterman, G. B., Hartman, H. R., and Rowntree, L. G. Toxic Nephritis in Pyloric and Duodenal Obstruction. Renal Insufficiency Complicating Gastric Tetany, *Arch Int Med* **32** 425 (Sept.) 1923

10 Jeghers, H., and Lerner, H. H. Syndrome of Alkalosis Complicating Treatment of Peptic Ulcer. Report of Cases with Review of Pathogenesis, Clinical Aspects and Treatment, *New England J Med* **214** 1236 (June 18) 1936

11 Grant, S. B. Tetany. A Report of Cases with Acid-Base Disturbance, *Arch Int Med* **30** 355 (Sept.) 1922

12 Houghton, L. W., Venables, J. F., and Lloyd, N. L. Toxemia Following Obstruction Near Pylorus, *Guy's Hosp Rep* **75** 149 (April) 1925

13 McArthur, C. B., and Payne, W. W. Alkalosis in Congenital Hypertrophic Stenosis, *Lancet* **1** 286 (March 5) 1930

14 Pfeiffer, D. B. Alkalosis Due to Pyloric Stenosis Simulating Nephritic Uremia, *Ann Surg* **92** 900 (Nov.) 1930

15 Butler, A. M. Acidosis or Alkalosis in Infants and Children with Gastrointestinal Disturbances, Chronic Nephritis, and Diabetes Mellitus, *M Clin North America* **18** 1205 (Jan.) 1935

16 MacCallum, W. G., Lintz, J., Vremilye, H. N., Leggett, T. H., and Boas, E. The Effect of Pyloric Obstruction in Relation to Gastric Tetany, *Bull Johns Hopkins Hosp* **31** 1 (Jan.) 1920

17 Eusterman, G. B., and Balfour, D. C. The Stomach and Duodenum, Philadelphia, W. B. Saunders Company, 1935, p. 288

18 Kim, T. Ueber die Saure-Basengleichgewicht regulierende Funktion der Leber, *J Chosen M A* **22** 1 (Jan.) 1932, abstracted, *Chem Abstr* **26** 6002 (Nov 20) 1932

19 MacNider, W. deB. The Influence of Liver Degeneration and Recuperation on the Acid-Base Equilibrium of the Blood, *J Pharmacol & Exper Therap* **50** 108 (Jan.) 1934



liver has an important role in maintaining the acid-base balance of the body. Sensitivity to alkali as a cause of alkalosis was suggested by Rafsky and his co-workers<sup>20</sup>. They recommended that small doses be used at the onset of treatment, followed by gradually increasing doses, with special precautions for patients with a history of allergy.

#### ACID-BASE BALANCE

The biochemical literature on the subject of acid-base balance is extensive and diffuse, and it is not generally available to the clinician. As a certain knowledge of this field is necessary for the evaluation of the acid-base disturbances encountered in patients and for the interpretation of the data presented in this paper, a brief review of the biochemical background is presented.

The term "acid-base balance" may be defined as the equilibrium between the anions and the cations in the body. More commonly, the term refers to that equilibrium in the blood, for the acid-base balance of the blood reflects that of the body. Although numerous kinds of ions are involved in this balance, a picture of it that is adequate for most purposes will be given by the determination of two characteristics of the blood: the  $p_H$  and the carbon dioxide content. The latter is made up of two components, the serum bicarbonate,  $\text{BHCO}_3$ , and the carbonic acid,  $\text{H}_2\text{CO}_3$ . These can be calculated from the values of  $p_H$  and carbon dioxide content by means of the Henderson-Hasselbalch equation:

$$p_H = pK' + \log \frac{\text{BHCO}_3}{\text{H}_2\text{CO}_3}$$

In this equation  $pK'$  is the negative logarithm of  $K'$ , which is the apparent dissociation constant for carbonic acid. The  $pK'$  for human serum is 6.10 at 38°C.<sup>21</sup> The carbonic acid component may be expressed conveniently as the partial carbon dioxide tension of the blood,  $p\text{CO}_2$ , measured in terms of millimeters of mercury. This may be done by applying an appropriate factor which includes the solubility coefficient of carbon dioxide in blood serum.

Although a knowledge of the three values—those of  $p_H$ , of serum bicarbonate and of partial carbon dioxide tension—is necessary for a full characterization of the acid-base balance, that of serum bicarbonate is the most informative single value. It frequently is called the "alkali reserve," because it closely mirrors the amount of available alkali in the entire body.

20 Rafsky, H. A., Schwartz, J., and Kruger, A. W. The Relation of Alkalosis to Peptic Ulcer, *J. A. M. A.* **99** 1582 (Nov. 5) 1932.

21 Hastings, A. B., Sendroy, J., Jr., and Van Slyke, D. D. Studies of Gas and Electrolyte Equilibria in Blood. XII. The Value of  $pK'$  in the Henderson-Hasselbalch Equation for Blood Serum, *J. Biol. Chem.* **79** 183 (Sept.) 1928.

*Acidosis and Alkalosis*—The disturbances of acid-base balance encountered in patients may be (1) respiratory or (2) metabolic in origin

1 The respiratory changes are characterized chiefly by an increase or a decrease of the carbonic acid, due to abnormalities of respiratory activity. These changes may be (a) an excess of carbon dioxide (respiratory acidosis) due to underventilation or (b) a deficit of carbon dioxide (respiratory alkalosis) due to hyperventilation

2 The metabolic changes are caused chiefly by an increase or a decrease of the available alkali of the body. These changes may be (a) an excess of acid (metabolic acidosis) due to the addition of fixed acid to the body or the loss of alkali or (b) an excess of alkali (metabolic alkalosis) due to the addition of alkali or the loss of fixed acid from the body

TABLE 1—Changes in the Components of the Acid-Base Balance Occurring in Various Kinds of Acidosis and Alkalosis

Condition	Cause	pH	Bicar- bonate	Carbonic Acid
Respiratory alkalosis (CO <sub>2</sub> deficit)	Hyperventilation	Increased	Slightly decreased	Decreased
Respiratory acidosis (CO <sub>2</sub> excess)	Underventilation	Decreased	Slightly increased	Increased
Metabolic alkalosis (alkali excess)	Addition of alkali or loss of fixed acid	Increased	Increased	Slightly increased
Metabolic acidosis (alkali deficit)	Addition of fixed acid or loss of alkali	Decreased	Decreased	Slightly decreased

The changes occurring in the acid-base balance in these conditions are presented in table 1. In addition to the four simple conditions, combinations may occur

*Interpretation of Acid-Base Changes by Triaxial Graphing*—The nature of clinical disturbances of the acid-base balance may be readily understood when the disturbances are represented as pathways, which denote not only the degree but also the direction of displacement of the acid-base balance. These pathways may be constructed by plotting the acid-base data on triaxial graph paper<sup>22</sup> as described by Hastings and

<sup>22</sup> Triaxial graph paper, on which the coordinates are equally spaced at 60 degree angles, is adapted for plotting data which are related according to the equation  $ax + by + cz = K$ . The Henderson-Hasselbalch equation,

$$pH = pK' + \log \frac{BHCO_3}{H_2CO_3}$$

is suited for such graphing when it is placed in the form

$$pH - \log BHCO_3 + \log H_2CO_3 = pK'$$

Log pCO<sub>2</sub> may be substituted for log H<sub>2</sub>CO<sub>3</sub> by including an appropriate factor

Steinhaus<sup>23</sup> Chart 1 presents data on the acid-base balance for 2 patients graphed by this method. It will be seen that any given point on the graph indicates the values of  $p_{\text{H}}$ , of serum bicarbonate and of partial carbon dioxide tension. The four major types of acid-base disturbance are shown as pathways, their positions having been determined empirically by clinical and experimental observations. One may thus readily evaluate the roles of respiratory and metabolic factors in producing any given disturbance of acid-base balance.

*Values Needed to Evaluate Disturbances of Acid-Base Balance*—It is common practice in evaluation of disturbances of the acid-base balance to determine the carbon dioxide content only. This value alone is not adequate, for, as has been stated, without the value for the  $p_{\text{H}}$  also, the carbon dioxide content cannot be separated into its two components, serum bicarbonate and partial carbon dioxide tension. From

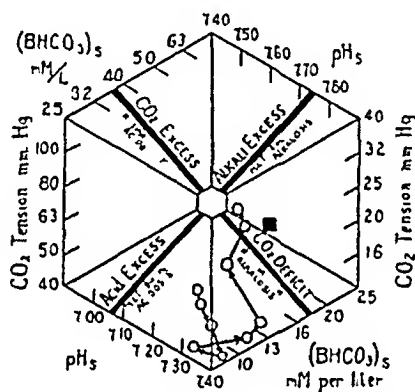


Chart 1—Triaxial graphing of data on the acid-base balance. Any given point indicates the appropriate values of  $p_{\text{H}}$ , serum bicarbonate and partial carbon dioxide tension. The position of the three sets of coordinates may be understood by referring to the figures of a clock. The constant  $p_{\text{H}}$  lines run in the direction of 6 and 12 o'clock, the constant serum bicarbonate lines, in the direction of 4 and 10 o'clock, and the constant partial carbon dioxide tension lines, in the direction of 2 and 8 o'clock. The small center hexagon represents the normal range of the acid-base balance. The four major pathways of displacement of the acid-base balance are indicated by heavy lines.

The black square indicates the data for F S, in whose case the carbon dioxide content was normal (because of a high bicarbonate content in the serum and a low partial carbon dioxide tension counterbalancing one another) but the  $p_{\text{H}}$  was greatly elevated. The ten circles indicate data for L G for twenty-one days at intervals of one to three days, showing recovery from metabolic acidosis which was complicated by respiratory alkalosis. In the first five determinations, the  $p_{\text{H}}$  was normal, although the carbon dioxide content was low (made up of a low bicarbonate content in the serum and a low partial carbon dioxide tension).

<sup>23</sup> Hastings, A. B., and Steinhaus, A. H. A New Chart for the Interpretation of Acid-Base Changes and Its Application to Exercise, *Am J Physiol* 96: 538 (March) 1931.

the foregoing paragraphs it will be seen that the direction of displacement of the acid-base balance cannot be evaluated without these values

The inadequacy of determining either the carbon dioxide content or the  $p_H$  alone will be further appreciated when it is realized that serious disturbances of the acid-base balance may occur in which one or the other of these values remains normal

For example, in F S (chart 1), a 70 year old woman, a disturbance occurred during alkali therapy, and the acid-base balance was displaced between the pathway of metabolic alkalosis and that of respiratory alkalosis so that an increased serum bicarbonate and a decreased partial carbon dioxide tension counterbalanced one another. The carbon dioxide content thereby remained normal (25.5 millimols per liter), but the  $p_H$  was markedly elevated ( $p_H$  7.59)

As a contrasting example, the following observations were made on L G, a 57 year old white woman who had impaired renal function. She was given ammonium chloride in the treatment of a urinary infection, and high grade metabolic acidosis developed in combination with respiratory alkalosis due to hyperventilation. This resulted in markedly decreased concentrations of serum bicarbonate and carbonic acid and therefore in an exceedingly low carbon dioxide content of the blood, but the  $p_H$  remained normal, namely,  $p_H$  7.40<sup>24</sup>. The results of ten determinations of the acid-base balance, made on L G over a period of twenty-one days, are presented in chart 1

The determination of serum chlorides is frequently desirable in studies of alkalosis, but it is not considered an essential procedure. A decrease of the serum chlorides has frequently been observed to accompany the increased carbon dioxide content in alkalosis, regardless of the cause. This effect depends on the fact that the total base concentration of the serum usually is maintained at a relatively constant level. The total base is combined, for the most part, with  $Cl^-$  and  $HCO_3^-$  ions. Consequently, a change in the concentration of one of these anions causes a compensatory and inverse alteration in the concentration of the other. Thereby, a normal electrolyte content and a normal osmotic pressure are preserved. This relation is illustrated by data on S K (no. 25 in the alkalosis series) in chart 2. It will be seen that the curves of the serum bicarbonate and of the serum chlorides are nearly mirror images of one another. Essentially the same picture may be produced by a loss of hydrochloric acid in pyloric obstruction, but here there is a compensatory rise of the bicarbonate content of the serum, which is derived from the ubiquitous carbonic acid. Exceptions to this complementary relation of the  $Cl^-$  and  $HCO_3^-$  may occur, as in the rare instances when the total base of the plasma is altered or when the anions of other acids enter the blood.

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24 This case is being reported in full elsewhere

### DAILY VARIATIONS IN THE ACID-BASE BALANCE DURING ALKALI THERAPY FOR PEPTIC ULCER

*A Material*—Determinations of the acid-base balance were made on cutaneous blood twice daily in 16 cases. The observations were commenced the day before the onset of a modified Sippy treatment and were continued morning and evening for a variable number of days, usually seven to fourteen. As nearly as possible, the daily dose of alkali powders was kept constant. Powders consisting of 2 Gm of sodium bicarbonate and 0.6 Gm of calcium carbonate were given every hour from 8:30 a. m. to 6:30 p. m. and every half hour from 7 to 9 p. m. Thus, sixteen powders were given daily, providing 32 Gm of sodium bicarbonate and 9.6 Gm of calcium carbonate. Ninety cubic centimeters of a mixture of milk and cream was given every hour from 7 a. m. to 7 p. m. In some instances three small bland feedings also were given. Any variations from this schedule

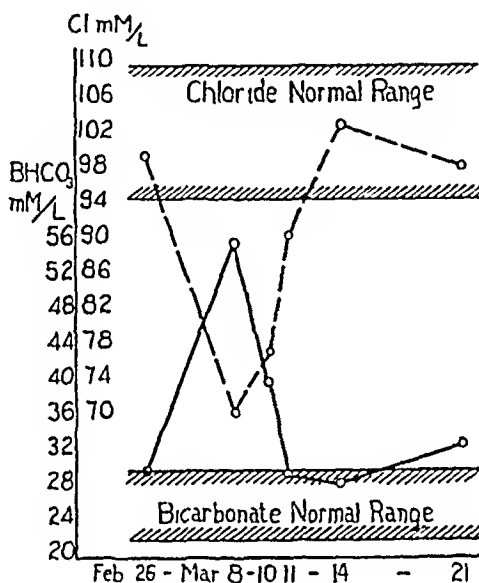


Chart 2 (patient 25 in the alkalosis series)—The inverse relation of serum bicarbonate and serum chlorides, in alkalosis

will be noted. Samples of blood for determinations of the acid-base balance were obtained at 8:30 a. m. and at 9:30 p. m.

The daily fluid intake and urinary output and the bicarbonate content and specific gravity of the twenty-four hour specimens of urine were determined on 2 patients. For each of these patients a three day period of restricted fluid intake was observed. Limitation of fluid intake could not be enforced to extreme degrees, because administration of the sixteen daily powders was continued, and water was necessary to swallow them. The hourly administration of the mixture of milk and cream was discontinued.

*B Methods*—The microtechnique of Shock and Hastings<sup>25</sup> was used for determinations of the acid-base balance, for with this method venipuncture is not

<sup>25</sup> Shock, N. W., and Hastings, A. B. Studies of the Acid-Base Balance of the Blood. I. A Microtechnique for the Determination of the Acid-Base Balance of the Blood, *J. Biol. Chem.* **104**: 565 (March) 1934.

necessary. A 0.1 cc sample of whole blood taken from the finger tip under oil was used to determine the percentage of erythrocytes by means of the hematocrit, the  $p_{\text{H}}$  colorimetrically by the method of Hastings and Sendroy<sup>26</sup> and the carbon dioxide content of the whole blood by the method of Van Slyke and Neill<sup>27</sup>. Determinations were usually made in triplicate. From these experimental data the bicarbonate content of the serum and the partial carbon dioxide tension were calculated with the nomographic chart designed for this purpose by Hastings and Shock<sup>28</sup>.

Cutaneous blood closely approximates arterial blood in composition<sup>29</sup>. Saito<sup>30</sup> has shown that cutaneous blood can be used as well as venous blood for following the acid-base changes in cases of acidosis or of alkalosis. The normal range for the acid-base balance of cutaneous blood is  $p_{\text{H}}$  7.35 to 7.47, serum bicarbonate 23 to 30 millimols per liter and partial carbon dioxide tension 40 to 50 mm of mercury (Shock and Hastings<sup>31</sup>).

*C Results*—Data for 3 patients, which are considered characteristic of the group, are presented in chart 3. With 1 exception all patients studied remained free from symptoms of alkalosis, not only during the periods of intensive biochemical observation but also during their subsequent observation in the hospital and the outpatient clinic. In all cases there was a shift of the acid-base balance toward the alkaline side. There was usually an elevation of the  $p_{\text{H}}$  to 7.50 to 7.54 and an elevation of the serum bicarbonate to 36 to 38 millimols per liter. Thus, it may be said that all patients receiving the Sippy type of therapy have some degree of chemical alkalosis, although clinical alkalosis seldom develops.

A distinct tolerance to alkali developed in most patients. Usually the greatest displacement of the acid-base balance occurred on the evening of the third day of treatment. A few patients reached the peak on the evening of the second day. Thereafter, the daily displacement of the acid-base balance, especially of the bicarbonate content of

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26 Hastings, A. B., and Sendroy, J., Jr. Studies of Acidosis. Colorimetric Determination of Blood  $p_{\text{H}}$  at Body Temperature Without Buffer Standards, *J Biol Chem* **61** 695 (Oct.) 1924.

27 Van Slyke, D. D., and Neill, J. M. Determination of Gases in Blood and Other Solutions by Vacuum Extraction and Manometric Measurement, *J Biol Chem* **61** 523 (Sept.) 1924.

28 Hastings, A. B., and Shock, N. W. Studies of the Acid-Base Balance of the Blood. II. A Nomogram for Calculation of Acid-Base Data for Blood, *J Biol Chem* **104** 575 (March) 1934.

29 Lundsgaard, C., and Møller, E. Investigations on the Oxygen Content of Cutaneous Blood (So-Called Capillary Blood), *J Exper Med* **36** 559 (Nov.) 1922.

30 Saito, K. Gaseous Content of Arterial, Cutaneous and Venous Blood in Normal State, Acidosis, and Alkalosis, *J Biol Chem* **25** 89 (Jan.) 1937.

31 Shock, N. W., and Hastings, A. B. Studies of the Acid-Base Balance of the Blood. III. Variation in the Acid-Base Balance of the Blood in Normal Individuals, *J Biol Chem* **104** 585 (March) 1934.

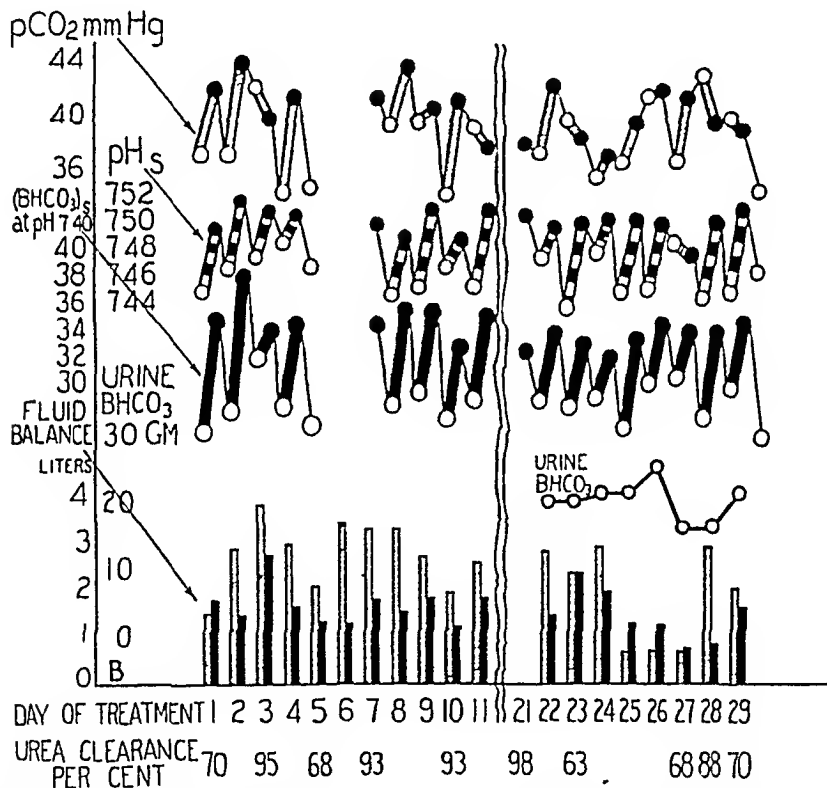
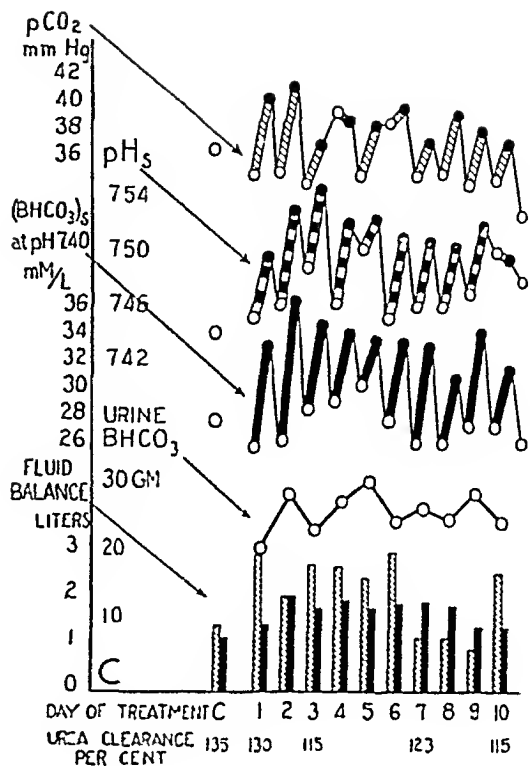
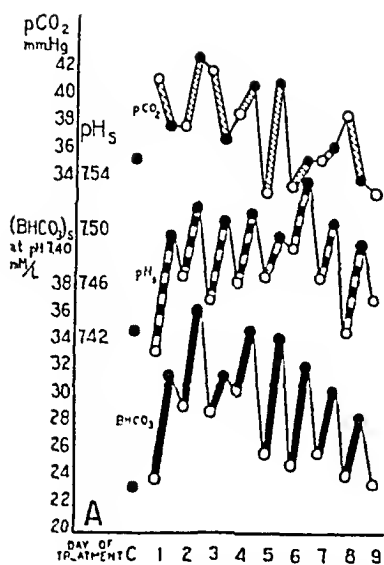


Chart 3—*A* (D S), data on the acid-base balance determined twice daily, demonstrating the development of a tolerance to alkalis during daily ingestion of sixteen powders (32 Gm of sodium bicarbonate and 96 Gm of calcium carbonate) The open-faced circles indicate morning determinations, the solid circles indicate evening determinations The heavy bars denote the shift occurring during the day period of ingestion of powder, the light lines denote the degree of recovery during the night *B* (M S), data on the acid-base balance determined twice daily, as in chart 3 *A* The fluid intake is indicated by shaded columns, the urinary output, by solid columns Sixteen alkaline powders were taken daily (32 Gm of sodium bicarbonate and 96 Gm calcium carbonate) *C* (D W), data on the acid-base balance determined twice daily, demonstrating the development of tolerance to alkalis

the serum, tends to decrease. This trend is best seen in the case of D S (chart 3 A). In the case of M S (chart 3 B), the acid-base balance was determined twice daily during thirty days of treatment (Chemical observations were interrupted twice, but the daily ingestion of alkali remained constant). The peak of the acid-base displacement occurred on the evening of the third day. D W (chart 3 C) reached the peak on the second day.

The daily excretion of bicarbonate in the urine was found to vary from 17 to 27 Gm for M S (chart 3 B) and from 20 to 31 Gm for D W (chart 3 C). Excretion of bicarbonate was maintained during the three day periods of restriction of fluid intake, for, although the volume of urine was decreased, the urine became more concentrated. These data, together with the data for fluid intake and urinary output,

TABLE 2—*Effect of Limitation of Fluid Intake on Urinary Excretion of Bicarbonate*

		24 Hour	24 Hour Specimen of Urine		
		Fluid	Volume,	Specific	Bicarbonate
		Intake,			
		Cc	Cc		Gm
I M S (chart 3A)					
(a) Daily average when water was taken as desired		2,880	1,790	1 020	21 5
(b) Daily average when fluid was restricted for a 3 day period		758	1,240	1 026	22 4
II D W (chart 3B)					
(a) Daily average when water was taken as desired		2,670	1,700	1,020	26 1
(b) Daily average when fluid was restricted for a 3 day period		1,120	1,538	1 025	27 6

are summarized in table 2. With the exception of the periods of restriction, the average daily fluid intake and output were somewhat greater than normal. During the periods of restriction the volume of urine exceeded the fluid intake. Except for great thirst, no symptoms were noted during these periods.

#### DAILY VARIATION OF THE ACID-BASE BALANCE DURING THE DEVELOPMENT OF CLINICAL ALKALOSIS

In 1 of the patients studied, clinical alkalosis developed during the period of observation.

C B, a 43 year old white man, had been receiving a modification of the treatment for ambulatory patients with ulcer, including small doses of alkali, for six months. As the ulcer had not healed, he was hospitalized for intensive alkali therapy. The acid-base balance was determined twice daily from the day the alkali therapy was started until recovery from the ensuing alkalosis had occurred. The data are presented graphically in chart 4.



On the evening of the third day of treatment, the bicarbonate content of the serum had reached 46.5 millimols per liter, and the  $p_{\text{H}}$  was 7.68. This was a far greater degree of chemical alkalosis than was seen in the other patients studied (chart 3). Although this was the greatest displacement of the acid-base balance observed in this patient, the onset of symptoms did not occur until the following (fourth) day, and symptoms were not marked until the fifth day. On the fourth day symptoms were vague and unobtrusive, namely, a distaste for powders and for milk and cream. It so happened that on this day only nine of the usual sixteen powders were taken, because a fluoroscopic examination of the stomach had been

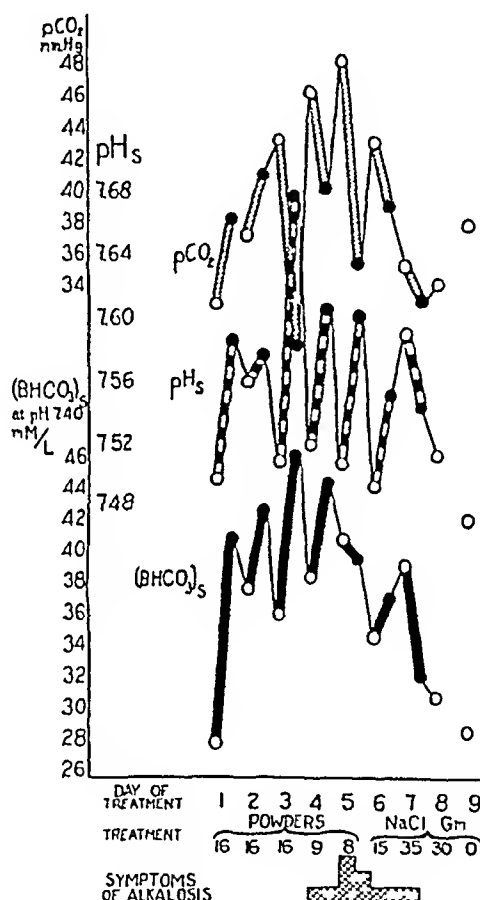


Chart 4 (C B) —Data on the acid-base balance determined twice daily during development of and recovery from clinical alkalosis. Note that the symptoms were not correlated with the degree of chemical alkalosis.

scheduled and the patient fasted until 3 p.m. Severe symptoms developed during the afternoon of the fifth day—headache, lassitude, nausea and vomiting, in addition to a continuation of the distaste for powders and for milk and cream. Administration of powders was discontinued at 4 p.m., eight powders having been taken. In spite of the more severe symptoms on the fifth day, the acid-base balance was less disturbed than on the two previous days.

A slow, continuous infusion of a mixture of milk and cream through an indwelling stomach tube was started on the sixth day. Five grams of sodium chloride was added to each liter of the mixture. At the end of the second day

of this treatment (seventh day of treatment for ulcer) all symptoms and chemical evidence of alkalosis had disappeared

By plotting the data for C B triaxially (chart 5) one sees that the direction of the daily displacement of the acid-base balance changed during the development of alkalosis. On the first day of treatment the direction paralleled the pathway of metabolic alkalosis. On the third day the displacement was greatest of all, but its direction had changed so that it ran about midway between the pathway of metabolic alkalosis and that of respiratory alkalosis. On the fifth day, when symptoms were most marked, the direction had changed even more, so that the direction of the day's displacement now paralleled the pathway of respiratory alkalosis, although the acid-base balance for the entire day was removed far out along the pathway of metabolic alkalosis. Thus, the direction of

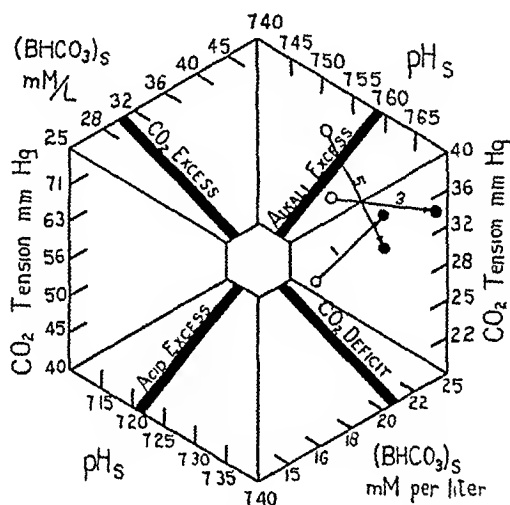


Chart 5 (C B) —Triaxial graphing of data on the acid-base balance demonstrating a change in the direction of the daily displacement accompanying the development of clinical alkalosis. The open-faced circles indicate morning analyses, solid circles, evening analyses, the arrows, the direction of the day's displacement, and the numbers above the arrows, the day of treatment.

the fifth day's displacement crossed the pathway of metabolic alkalosis at nearly right angles.

This shift in the direction of displacement is interpreted as a protective mechanism of the body, which prevents the serum bicarbonate from departing too far from normal. The change in direction was due to a deficit of carbon dioxide (or respiratory alkalosis) complicating the metabolic alkalosis and was caused by hyperventilation.

#### LACK OF CORRELATION BETWEEN CLINICAL AND CHEMICAL ALKALOSIS

The symptoms of clinical alkalosis are variable. The earliest symptoms may be simply a distaste for powders and food (especially milk

and cream) Lassitude, weakness, headache, nausea and vomiting may be early symptoms, or they may appear later All variations from mild drowsiness to stupor and coma have been observed Mental symptoms varying from slight changes in personality (such as irritability and lack of cooperation) to disorientation and irrationality have been noted The more severe mental symptoms were seen especially in older patients with evidence of arteriosclerosis Tetany and muscular twitchings, described by several authors, have been notably absent Shock and Hastings<sup>32</sup> stated the belief that a marked decrease in partial carbon dioxide tension is the cause of tetany in disturbances of the acid-base balance This would occur primarily in hyperventilation

A striking lack of correlation has been observed between the severity of symptoms and the degree of chemical alkalosis Data for 9 selected patients (table 3) illustrates this In patients F C and M V characteristic symptoms of alkalosis developed during treatment for ulcer The values for the blood of F C, however, were entirely normal, and those for the blood of M V only slightly elevated, the elevation being no greater than that usually observed for patients receiving a Sippy type of treatment In contrast to these, patients 26 and 22 had no symptoms during the period when the acid-base balance shifted markedly to the alkaline side The values for patient 18 are characteristic of those in the usual case in which severe symptoms accompanied the marked chemical alkalosis, however, it will be noted that the chemical alkalosis was less severe than that in patients 26 and 22, who had no symptoms In patient 24 (see also chart 4) the symptoms and chemical composition of the blood were not correlated from day to day In patient 8 the symptoms may well have been related to the retention of nitrogenous products rather than to the alkalosis These findings suggest that symptoms of alkalosis do not depend on a definite threshold of chemical alkalosis

#### URINARY EXCRETION OF SOLIDS DURING TREATMENT FOR PEPTIC ULCER

In addition to their normal function, the kidneys are required to assume a considerable extra burden during the Sippy type of treatment The excretion of large amounts of bicarbonate has been demonstrated It is likely that the excretion of the basic ions is proportionately even greater, for, of that part of the ingested alkali which is used to neutralize gastric acidity, the bicarbonate escapes as gaseous carbon dioxide by belching, thereby leaving the basic ions for the kidneys to excrete As a measure of this extra work, the total solids excreted by the kidneys

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32 Shock, N W, and Hastings, A B Studies of the Acid-Base Balance of the Blood IV Characterization and Interpretation of Displacement of the Acid-Base Balance, *J Biol Chem* **112** 239 (Dec) 1935

was determined. Similar determinations were made on a group of nonulcerous patients, as controls.

The concentration of solids in the twenty-four hour specimen of urine was estimated by multiplying the last two figures of the specific gravity by 2.3 (Haeser's coefficient<sup>33</sup>). The total solids was calculated in grams by multiplying this product by the volume of the specimen (in

TABLE 3—*Lack of Relation of Symptoms to Chemical Alkalosis*

Patient (Alka- losis Series)	Date	Symptoms	pH	Carbon Dioxide Content, mM/L	Serum Chlor- ides, mM/L	Urea Nitrogen, Mg per 100 Gm	Comment
F. C. (not in alkalosis series)	May 11, 1935	Headache, fatigue, list- lessness	7.40	28.1			Symptoms of alkalo- sis while receiv- ing alkali therapy, but normal blood chemistry
M. V. (not in alkalosis series)	Sept. 17, 1934	Headache, nausea, vomit- ing, distaste for powder	7.53	33.1			Typical symptoms of alkalosis while receiving alkali therapy, but pH and CO <sub>2</sub> only slightly elevated
26	Feb. 25, 1937	No symptoms	7.63	46.0	80		Marked chemical alkalosis without symptoms
22	Nov. 2, 1933	No distress	7.62	52.4		28.4	Same as for patient 26
18	Nov. 4, 1933	Still no distress					
	Jan. 21, 1934	Swelling, irritability, disorientation	7.56	44.4			Severe symptoms with less chemical alkalosis than in patients 25 and 22
25	March 8, 1937	Drowsiness	7.73	55.2	70	45.0	See chart 2
4	June 1, 1933	Drowsiness from which patient was easily aroused, irritability	7.65	35.1			
24	June 16, 1935	No symptoms	7.68	40.0			Lack of correlation between symptoms and degree of shift of acid-base balance from day to day (see charts 4 and 5)
	June 17, 1935	Distaste for powder and for milk and cream	7.60	40.5		21.6	
	June 18, 1935	Lassitude, severe headache, nausea and vomiting	7.60	35.3			
8	June 17, 1932	Disorientation, irritability	7.69	49.2		78.0	Symptoms and re- tention of nitrogen progressing to fatal end, while acid base balance improved
	June 18, 1932	Coma, convul- sions	7.59	46.0		90.0	
	June 19, 1932	Patient died in coma	7.50	31.4		98.0	

liters). The total solids excreted in the urine was then expressed in terms of grams per kilogram of body weight per twenty-four hours.

The total twenty-four hour urinary excretion of solids was determined twenty-five times for 3 patients undergoing treatment for ulcer. It was found to vary from 0.9 to 1.5 Gm. per kilogram of body weight, the average being 1.24 Gm. Determinations on 95 twenty-four hour

<sup>33</sup> Seifert, O., and Mueller, F. Manual of Physical and Clinical Diagnosis, ed. 2, translated by E. C. Andrus, Philadelphia, J. B. Lippincott Company, 1934, p. 186.

specimens from the control series of 6 persons<sup>34</sup> showed the total solids to vary from 0.3 to 1 Gm per kilogram per twenty-four hours, the average being 0.63 Gm. Thus, the average urinary excretion of solids of patients undergoing treatment for ulcer was nearly twice as great as that of patients in the control group. These data are presented graphically in chart 6.

A CLINICAL STUDY OF TWENTY-EIGHT PATIENTS IN WHOM  
CLINICAL ALKALOSIS DEVELOPED DURING TREATMENT  
FOR PEPTIC ULCER

During a ten year period (1928 to 1937), moderate to severe clinical alkalosis developed in 28 patients undergoing treatment for ulcer at the

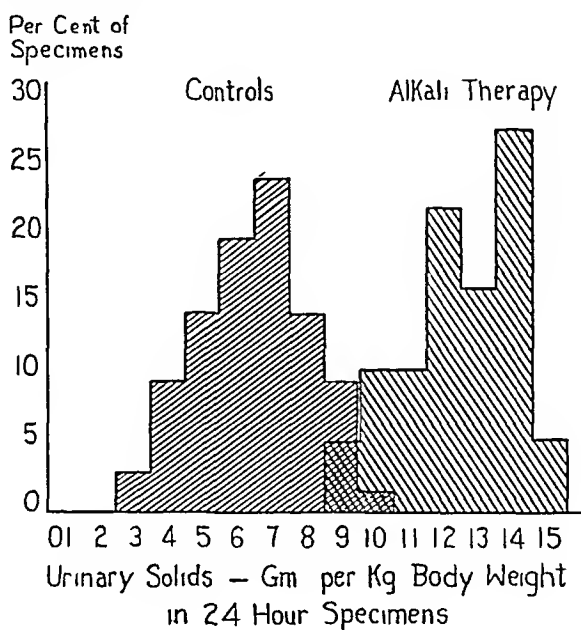


Chart 6—The daily excretion of solids by the kidney during alkali therapy (25 specimens) as compared to that in a control group (95 specimens)

University of Chicago Clinics. The case histories of these patients were critically reviewed with the special purpose of evaluating any evidence for the existence of renal damage prior to the onset of alkalosis. The group consisted of 26 men and 2 women. The ages ranged from 35 to 75 years, the average being 52 years. Nine patients were 60 years of age or older. Five patients had gastric ulcers, and 24 had

<sup>34</sup> The control group was made up of 2 patients with pulmonary tuberculosis on high caloric diets, 1 patient with tuberculous pleural effusion during the resorption stage, 1 patient with arthritis with fever, 1 patient with advanced Hodgkin's disease with fever and 1 normal man engaged in his usual occupation.

duodenal ulcers (One had both gastric and duodenal ulcers) Fourteen patients had moderate to severe stenosis

Nineteen patients showed evidence of preexisting renal damage The data for 3 additional patients were suggestive of renal damage but were not conclusive Of the remaining 6 patients, the data for 4 were

TABLE 4—*Evidence of Renal Damage Found in the Alkalosis Series*

Case No	High Blood Pressure	Low Urea Index	Anemia	Arteriosclerosis	Prostatism	Other Findings	Autopsy Data*	Summary
1	+					Bilateral renal calculi		++
3	+	+	+	+				++++
4			+	+				++
5		+	+					++
6	+				+			++
7	+				+			++
8	+					Nephrectomy	Old nephrectomy, remaining kidney showing subacute interstitial nephritis	+++
9	+			+	+		Pyelonephritis, essential hypertension	++++
11				+				+
15		+						+
17		+				Renal colic		++
18	+	+		+		Calcified blood vessels, albumin and erythrocytes in urine, urea nitrogen in blood, 41 mg per cc		++++
19	+							+
20		+	+					++
21		+	+				Arteriosclerotic kidneys	+++
22	+							+
23		+	+					++
24	+		+	+	+		Arteriosclerosis	+++
25	+	+						++
26	+			+				++
27	+		+	+			Atrophy of kidneys, arteriolar arteriosclerosis	++++
28	+		+		+			+++
Total	14	9	9	8	5	4	5	

\* In addition to the 5 autopsies, there were 5 deaths without autopsy within one year of the attack of alkalosis Of the 10 deaths, 3 were attributed to the alkalosis

considered inadequate to form conclusions, and that for the other 2 suggested normal kidneys but lacked the completeness desirable to prove that the kidneys were unimpaired Unfortunately, careful studies of the renal function were not made routinely before starting therapy The evidence for preexisting renal impairment in the 19 patients classified as having suffered previous damage to the kidneys and in the additional 3 suspected is summarized in table 4 The data are listed under seven

criteria In the majority of cases two to five of the criteria were present Anemia was present in 9 cases, but in all of them other criteria were present also That anemia in itself can be a cause of low renal function has long been known In 1915 Mosenthal<sup>35</sup> observed that in severe anemia, whether of primary or secondary type, tests of renal function give results similar in all respects to those described in cases of contracted kidney in the advanced stages The cure of the anemia was noted to be followed by great improvement in the renal function Christian,<sup>36</sup> Stieglitz,<sup>37</sup> Fishberg<sup>38</sup> and others have noted similar phenomena, especially in pernicious anemia Fishberg stated the belief that the low renal function in anemia is due to malnutrition of the kidney cells and more particularly to a reduced supply of oxygen

#### COMMENT

Various phases of the present investigation emphasize the great importance of renal function in the causation of alkalosis It has been demonstrated that a greatly increased burden is placed on the kidneys during alkali therapy Studies of fluid balance show that during treatment for ulcer, fluid intake and urinary output are increased Some of the patients commented on the frequency of urination, especially the nocturia, which they experienced Because of the likelihood that the kidneys might require a volume of water greater than normal to perform their extra work, three day periods of limitation of fluid were instituted to note whether renal compensation would fail In the 2 patients so studied, the kidneys were able to continue their function in spite of this handicap, but the body went into a negative fluid balance during these periods

Estimation of the total urinary excretion of solids suggest that the kidneys' work is nearly doubled during alkali therapy It is not surprising, then, that diseased kidneys may fail in this task Kidneys with a low functional reserve may be able to perform the work required by normal life without showing evidence of strain or of disease, but when the added burden of alkali therapy is imposed on them their functioning may prove inadequate, and alkalosis may ensue The situation is analogous to that of a heart with a low functional reserve which carries the patient through the ordinary activities of life without effort or

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35 Mosenthal, H O Renal Function as Measured by the Elimination of Fluids, Salt, and Nitrogen, and the Specific Gravity of the Urine, *Arch Int Med* **16** 733 (Nov) 1915

36 Christian, H A Renal Function in Pernicious Anemia as Determined by Dietary Renal Tests, *Arch Int Med* **18** 429 (Oct) 1916

37 Stieglitz, E J Disturbances of Renal Function in Pernicious Anemia, *Arch Int Med* **33** 58 (Jan) 1924

38 Fishberg, A M Hypertension and Nephritis, ed 3, Philadelphia, Lea & Febiger, 1934

evidence of disease but which decompensates when an additional burden, such as pregnancy or severe infection, is placed on it

Analysis of the clinical data for 28 patients with alkalosis further confirms the opinion that impaired renal function is of the highest etiologic significance in alkalosis. In the majority of the patients there was a correlation between preexisting renal disease and the development of alkalosis. Most of the patients were in the older age groups, in which a high incidence of arteriosclerotic renal disease may be expected. It is unfortunate that comprehensive studies of renal function were not made routinely before the onset of alkali therapy. If such studies were made, they probably would show that alkalosis develops only in patients with either definite renal disease or a low renal reserve. Exceptions may occur in cases of pyloric obstruction in which there is an excessive loss of gastric contents.

In most cases low renal reserve will remain undetected unless especially sought. Evidence of the condition may not appear on the usual routine clinical study, nor will a history of renal disease necessarily be present. Special studies of renal function are necessary. Which one of the many available tests of renal functions is best suited to measure the function of the kidneys with special reference to their ability to carry the burden of alkali therapy? A direct answer to this question is not available. Wilkinson and Jordan<sup>39</sup> have successfully used the sulfate clearance test for this purpose. Alving and Van Slyke<sup>40</sup> have shown that, in general, the urea clearance test measures the function of excreting nitrogen, while concentration tests measure the function of excreting mineral salts. Freyberg<sup>41</sup> compared the efficiency of most of the popular tests of renal function. He concluded that only during the concentration tests are conditions such that the renal function is measured while the kidneys are under functional strain and that therefore it is the only test designed to measure maximal function. The concentration test registers impairment of function when other tests do not, and it is therefore the most sensitive measure of renal efficiency. The urea clearance test may give a better conception of the degree of renal impairment, but it is considerably less sensitive in detecting early impairment of function.

It is not enough to exercise great care in administering alkalis to patients with evidence of renal disease. Among patients with ulcers those with low renal reserve must also be discovered and treated cautiously if alkalosis is to be avoided. Therefore, before starting intensive alkali therapy for any patient, a study of the functioning of

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39 Wilkinson, S. A., and Jordan, S. M. Significance of Alkalosis in Treatment of Peptic Ulcer, *Am J Digest Dis & Nutrition* **1** 509 (Sept.) 1934

40 Alving, A. S., and Van Slyke, D. D. The Significance of Concentration and Dilution Tests in Bright's Disease, *J Clin Investigation* **13** 969 (Nov.) 1934

41 Freyberg, R. H. The Choice and Interpretation of Tests of Renal Efficiency, *J A M A* **105** 1575 (Nov 16) 1935



his kidneys while under functional strain is indicated. If alkali therapy is to be prolonged, interval studies of renal function are worth the effort. Special care is also indicated in alkali therapy following hemorrhage.

Some experiments suggest that the prolonged administration of alkali may produce damage to the kidneys. Addis and his associates<sup>42</sup> found that prolonged administration of alkalis to rats produced gross or microscopic hematuria in all cases, but at autopsy no lesions were noted in the kidneys. Nuzum and his associates<sup>43</sup> showed that long-continued alkalinization caused moderate hypertension and renal damage in rabbits. Stieglitz<sup>44</sup> stated the belief that during alkali therapy the excretion of alkaline urine is irritating and causes renal damage. On the other hand, Kellert<sup>45</sup> gave rabbits intravenous injections of sodium bicarbonate and failed to observe any injurious effects on the kidneys or any aggravation of preexisting experimental nephritis. Steele<sup>46</sup> reported a case suggesting that the prolonged administration of alkalis may produce renal damage and impaired function. The renal function, however, was not studied before the alkali therapy was started.

In 1 patient in the present series signs of essential hypertension with decreased renal function developed while alkali therapy was being administered.

Patient 22, a 31 year old man, was first given alkali treatment for an uncomplicated duodenal ulcer in April 1931. At that time his blood pressure was 128 systolic and 80 diastolic and 130 systolic and 86 diastolic on two occasions. The standard urea clearance was 60 before the administration of alkalis was begun and 42 after ten days of treatment. Clinical alkalosis was not present, and chemical alkalosis was not unusual. In October 1933, after having taken alkali powders most of the intervening time, he was readmitted to the hospital after a massive hemorrhage. At that time his blood pressure was 185 systolic and 110 diastolic. After five days of alkali therapy in the hospital, alkalosis developed. His blood pressure then was 200 systolic and 115 diastolic, and his standard urea clearance had dropped to 25. He recovered from the hemorrhage, the anemia and the alkalosis uneventfully. He has been followed in the clinic until the time of writing and has continued to show hypertension and low urea clearance. He has taken little alkali since 1933.

Clinical experience suggests that most patients tolerate alkali powders over long periods and escape without renal damage. It cannot

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42 Addis, T., MacKay, E. M., and MacKay, L. L. The Effect on the Kidney of the Long-Continued Administration of Diets Containing an Excess of Certain Food Elements, *J Biol Chem* **71** 157 (Dec.) 1926.

43 Nuzum, F. R., Seegal, B., Garland, R., and Osborne, M. Arteriosclerosis and Increased Blood Pressure, *Arch Int Med* **37** 733 (June) 1926.

44 Stieglitz, E. J. Alkalis and Renal Injury, *Arch Int Med* **41** 10 (Jan.) 1928.

45 Kellert, E. The Action of Intravenous Injections of Sodium Bicarbonate upon the Kidneys, *Am J M Sc* **167** 114 (Jan.) 1924.

46 Steele, J. M. Renal Insufficiency Developing During Prolonged Use of Alkalis, *J A M A* **106** 2049 (June 13) 1936.

be denied, however, that an occasional patient may sustain injury to his kidneys. Almost certainly, preexisting renal disease may be aggravated.

What are the factors which determine the symptoms of alkalosis? The lack of correlation between clinical alkalosis and chemical alkalosis, even in the same patient, suggests that symptoms do not depend on a definite threshold of chemical alkalosis. It is possible that symptoms may be related to a cumulative effect of a prolonged displacement of the acid-base balance. Wildman<sup>47</sup> suggested that they are related to a decrease of chlorides in the plasma. Because of the usual reciprocal relationship between serum bicarbonate and serum chlorides (chart 2), it is not possible to evaluate directly the effect of deviation of chlorides on the symptoms. Similarly, it is difficult to evaluate the effect of depletion of chlorides in cases in which deviation of acid-base balance is not present, for in such cases changes in water balance and in total base occur. Peters and Van Slyke<sup>48</sup> stated the belief that toxic symptoms arising in connection with depletion of chlorides are probably due to these factors rather than to the depletion of chlorides. It should be noted that in cases of heat cramp and heat exhaustion a marked diminution of serum chlorides occurs with minimal changes in the other constituents of the blood (Shoudy and Baetjer<sup>49</sup>) and that in these conditions the symptoms are different from those seen in alkalosis.

#### CONCLUSIONS

1 Tolerance to alkalis usually develops during the Sippy type of treatment for peptic ulcer.

2 In all patients receiving alkali therapy some degree of chemical alkalosis develops, but clinical alkalosis develops in few.

3 Symptoms of alkalosis are not correlated with the degree of chemical alkalosis present.

4 During alkali therapy the work of the kidney is greatly increased. The urinary excretion of solids was found to be nearly doubled.

5 In the patients in whom clinical alkalosis developed during alkali therapy for peptic ulcer a high incidence of preexisting renal damage was found.

Dr A. B. Hastings and Dr Lillian Eichelberger advised concerning the biochemical problems. Dr George F. Dick and Dr Walter L. Palmer permitted the use of clinical material.

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47 Wildman, H. A. Chloride Metabolism and Alkalosis in Alkali Treatment of Peptic Ulcer, *Arch Int Med* **43** 614 (May) 1929.

48 Peters, J. P., and Van Slyke, D. D. *Quantitative Clinical Chemistry*, Baltimore, Williams & Wilkins Company, 1932, vol. 1.

49 Shoudy, L. A., and Baetjer, A. M. Heat and Muscular Work, *Surg., Gynec. & Obst.* **62** 475 (Feb) 1936.

# STAPHYLOCOCCIC SEPTICEMIA

A REVIEW OF THIRTY-FIVE CASES, WITH SIX RECOVERIES,  
TWENTY-NINE DEATHS AND SIXTEEN AUTOPSIES

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Contrary to common opinion, the staphylococcus is the deadliest organism of general sepsis. This bacterium, universal in distribution and of extremely low virulence, is generally considered to be a secondary invader, leading a saprophytic existence on the skin and mucous membranes of the body and producing small pimples, furuncles and abscesses. It is not fully appreciated that at the same time it is also capable of producing the most dangerous of all septicemias. From the most insignificant site of infection, even a microscopic abrasion of the skin, the staphylococcus may invade and infect the blood stream, with a resulting fatal outcome due to the formation of septic embolic foci or abscesses in all the organs of the body, and with the occurrence particularly of septic bronchopneumonia, metastatic abscesses and degeneration of the kidneys, liver and heart.

The incidence of staphylococcic septicemia is also greater than is commonly thought. About two thirds of all cases of septicemia are due to the streptococcus, principally *Streptococcus haemolyticus*, Stevens<sup>1</sup> has made an estimate of 60 per cent and Brookhart<sup>2</sup> an estimate of 80 to 90 per cent. Rosenow Jr and Brown<sup>3</sup> have given the ratio of streptococcic septicemia to staphylococcic septicemia as 2:1. Neuhof and his co-workers<sup>4</sup> have estimated the incidence of streptococcic septicemia in comparison with that of staphylococcic septicemia as 3:2. In the present series, excluding the cases of septicemia due to *Streptococcus viridans* from the total number of cases of streptococcic septicemia, the

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1 Stevens, F. A., in Nelson Loose-Leaf Living Medicine, New York, Thomas Nelson & Sons, 1929, vol. 1, p. 1298.

2 Brookhart, E. B. Staphylococcic Septicemia, *M. Sentinel* **38** 9-12 (Jan.) 1930.

3 Rosenow, E. C., Jr., and Brown, A. E. Septicemia. A Review of Cases, 1934-1936 Inclusive, *Proc. Staff Meet., Mayo Clin.* **13** 89-93 (Feb. 9) 1938.

4 Neuhof, H., Aufses, A. H., and Hirshfeld, S. Pyogenic Sepsis. Survey of One Hundred and Fifty Cases, *Surg., Gynec. & Obst.* **58** 886-896 (May) 1934.

incidence of streptococcic septicemia in comparison with that of staphylococcic septicemia was 23:1 (80 cases of the former and 35 of the latter)

This study was prompted by the unusual occurrence of recovery<sup>6</sup> in 3 cases of staphylococcic septicemia during the spring and summer of 1937, by the fact that only 3 other patients with staphylococcic septicemia have recovered in the past eight years in the Mount Sinai Hospital, and, also, as stated in other reports, by a desire to encourage others in the care of patients with this desperate disease, for some of these patients do recover, sometimes when it is least expected

While it was thought at first that the records of this hospital would yield more than 35 cases of staphylococcic septicemia over the period studied, the rigid criteria accepted for the diagnosis of staphylococcic septicemia were more responsible for limiting the total number than any other factor. There were many cases of staphylococcic infection with severe toxemia, many cases of transient staphylococcic bacteremia and many cases in which blood cultures of the staphylococcus were obtained agonally from a patient dying of other causes wherein staphylococci secondarily invaded the blood stream owing to the patient's debilitated state. Such cases were discarded and not used in this report. It is well known that harmless transient staphylococcic bacteremia does occur without septicemia, and cases have been reported as occurring after minor surgical procedures, such as extraction of a tooth or tonsillectomy (Fischer and Gottdenker<sup>5</sup>)

In the selection of cases for this study, Kolmer's<sup>6</sup> definition of staphylococcic septicemia was chosen as the criterion. "an infection of the blood by staphylococci, their pathogenic presence and products in the blood, associated with infection of fixed tissues resulting in severe constitutional disturbances with the signs of sepsis." The blood may be invaded by pathogenic organisms without the appearance of any signs of infection, and for that state the term bacteremia is used instead of septicemia

#### MORTALITY

The mortality for staphylococcic septicemia is very high. It is a deadly disease, and in most cases when the diagnosis is made it is already beyond control. Some authors place the mortality as high as 90 per cent. Reimann,<sup>7</sup> reviewing the literature on infections, made the state-

5 Fischer, J., and Gottdenker, F. Ueber transitorische Bakterieneinschwemmung in die Blutbahn nach Tonsillektomie, *Wien klin Wchnschr* **49** 177 (Feb 7) 1936

6 Kolmer, J. A. Septicemia, *Ann Int Med* **8** 612-631 (Nov) 1934

7 Reimann, H. A. Infectious Diseases. Review of the Current Literature *Arch Int Med* **58** 329-370 (Aug) 1936

ment that the average mortality for the disease is 79 per cent Scott,<sup>8</sup> in a series of 79 cases, reported a mortality of 79 per cent Bean<sup>9</sup> reported 9 cases, with 1 recovery, a mortality of 89 per cent Neuhoof<sup>1</sup> divided his cases as follows those due to osteomyelitis (27 cases), with a 56 per cent mortality, and those due to carbuncle (17 cases), with an 82 per cent mortality MacNeal and Frisbee<sup>10</sup> reported the use of bacteriophage in 100 cases, with a mortality of 75 per cent These authors stated that prior to 1929 any case of staphylococcic septicemia in which two consecutive blood cultures gave positive results was invariably fatal Rosenow Jr and Brown<sup>3</sup> reported 29 cases, with a mortality of 66 per cent Lowenstein<sup>11</sup> reported the occurrence of 18 cases in nine years at the Jewish Hospital in St Louis, with only 3 recoveries

In the present 35 cases (for 1929 to 1937, inclusive) there were 29 fatalities and 6 recoveries (a mortality of 83 per cent) Certain factors definitely influenced the mortality rate, as for instance the presence of associated diseases There were 9 such cases 6 of diabetes mellitus, 2 of hypertensive cardiovascular disease and 1 of rheumatic carditis All of these patients died The age factor was also of importance, recovery occurred in none of the patients in the first decade of life The sthenic age group fared best, as shown in other reports Of the 6 who recovered, 5 were between the ages of 13 and 33 years, the sixth patient was 53 years old Although in the majority of cases (27) the septicemia originated from infections of the skin (e g, carbuncles, abscesses and furuncles) or of bone (acute osteomyelitis), only these two sites were involved in the cases in which recovery occurred, all other sites of origin were noted in fatal cases, e g, the prostate, sinuses and heart Twelve of our patients were females, and all died This was merely a coincidence in this series, the disease being no more fatal in females, although the incidence is higher in males In reviewing the series for the cause of this unusual occurrence, it was found that of the 12 females, 6 were very young, most of them being in the first decade of life, wherein the total mortality was highest, only 1 was in the favorable sthenic age group, wherein the most recoveries occurred Of the 12 females, 4 had diabetes mellitus All these factors added to the

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8 Scott, W J M The Principles of the Treatment of Septicemia, J A M A **105** 1246-1249 (Oct 19) 1935

9 Bean, H C Clinical Study of One Hundred and Nine Cases of Septicemia, M Sentinel **37** 679-686 (Dec) 1929

10 MacNeal, W J, and Frisbee, F C One Hundred Patients with Staphylococcus Septicemia Receiving Bacteriophage Service, Am J M Sc **191** 179-195 (Feb) 1936

11 Lowenstein, P S Staphylococcus Septicemia, Am J M Sc **181** 196-203 (Feb) 1931

gravity of the disease and denoted in this series that the females were in the group showing a more unfavorable prognosis—hence the high mortality

Certain complications during the course of the septicemia influenced the mortality, for example, the occurrence of staphylococcic meningitis. There were 7 such cases, all were fatal.

#### SEX AND AGE

The ratio of males to females was nearly 2 to 1 (23 males and 12 females). This is in accord with the ratio given for other series reported in the literature.

The age groups were as follows:

Age	Fatal Cases	No. of Recoveries
1 to 9	5	0
10 to 19	7	3
20 to 29	5	1
30 to 39	3	1
40 to 49	4	0
50 to 59	3	1
60 to 69	2	0
	—	—
	29	6

The disease occurs at all ages, from infancy to senility. The youngest patient was 1 year old and the oldest 69. The incidence was about the same throughout the age groups, possibly slightly higher in early age groups, owing to the increased incidence of osteomyelitis in childhood, but this was nearly offset by the increased incidence of infections of the skin in later life. Twenty-one patients were under 30 and 14 were over 30. In none of the females was the site of origin in the female generative tract, whereas in the males the disease not infrequently originated in this tract. Osteomyelitis was more prevalent in the younger age groups, 10 of the 13 patients being less than 20 years old, whereas infections of the skin were more common after the age of 20, 11 of the 14 patients being in that age group.

#### SITES OF INFECTION

*Skin*—There were 14 cases in which the portal of entry was the skin (5 females and 9 males, 3 being under 20 years of age and 11 over 20). Six patients had carbuncles, and 1 recovered, 4 had abrasions of the skin, and 2 recovered, 4 had abscesses or furuncles and 1 recovered. The total mortality for this group was 71 per cent.

In the 10 fatal cases the average length of life of the patients in this group after the blood culture was established as positive was five and one-half days

*Osteomyelitis*—There were 13 cases of osteomyelitis (7 females and 6 males, 10 being under 20 years of age and 3 over 20) There were 2 recoveries, the patients being 18 and 13 years old, respectively In the 11 fatal cases the average length of life after blood culture gave positive results was five days In 5 cases the infection originated in the tibia, with no recoveries, in 2 in the pubic bone, with 1 recovery, in 2 in the humerus, with 1 recovery, in 1 case in the os calcis and in 1 case in the mastoid bone, both being fatal The total mortality for this group was 85 per cent

*Prostatic Abscess*—There were 3 cases of prostatic abscess, and all were fatal The ages of the patients were 39, 30 and 54 years, respectively The average length of life after blood culture gave positive results was seven days

*Infection of the Nasal Sinuses*—There were 2 patients with infection of the nasal sinuses, both of them boys aged 12 and 17, respectively, 1 died three days and the other six days after surgical intervention Meningitis was the cause of death in both cases

*Miscellaneous Infections*—There were 3 other cases of infection, and all were fatal One originated in a dental infection in a 27 year old man with rheumatic carditis, 1 originated in pulmonary abscess in a 19 year old boy and 1 originated in staphylococcic endocarditis in a 37 year old man

#### DURATION OF THE DISEASE

Staphylococcic septicemia is a desperate disease and as a rule is quickly and violently fatal Often a patient succumbs before therapeutic procedures have had an opportunity to act If life can be maintained past the first week or ten days, the prognosis is greatly enhanced Of the 29 patients who died, 27 were in the hospital for a total of three hundred and forty days, or an average of twelve and one-half days This group lived a total of a hundred and fifty-five days after positive results of blood culture were established, or an average of five and seven-tenths days, the shortest duration of life being one day (osteomyelitis of the tibia in a girl aged 1 year) and the longest being fifteen days (osteomyelitis of the mastoid bone with terminal staphylococcic meningitis) The 2 other patients who died (considered separately because the behavior of the disease was unlike that of true staphylococcic septicemia) lived one hundred and eighty-five days in the hospital, or an average of ninety-two and one-half days One had chronic bacterial endocarditis (*Staphylococcus albus haemolyticus*), and the clinical course was more like that of endocarditis lenta than of staphylococcic septicemia The other had

rheumatic carditis with a dental infection which resulted in staphylococcic septicemia, death resulting from embolic septic bronchopneumonia due to staphylococci

For the 6 patients who recovered, the total period of hospitalization was four hundred and fifty-four days, or an average of seventy-six days. If one contrasts this average of seventy-six days with that of twelve and one-half days of life in the fatal cases, one can well appreciate the old clinical dictum that the longer a patient with staphylococcic septicemia lives, the more favorable the ultimate outcome. Positive results of blood culture were obtained for an average of fourteen days for this group of 6 patients, the shortest period being five days (a 54 year old man with an abscess of the leg and septic thrombophlebitis) and the longest continuous period being thirty-two days (a 33 year old man with a carbuncle on the back, case 1)

#### LABORATORY DATA

*Staphylococcus aureus haemolyticus* was responsible in 33 of the 35 cases and *Staph. albus haemolyticus* in 2 cases. The infections due to the latter organism were both fatal. 1 case of staphylococcic endocarditis and 1 of violently acute osteomyelitis of the os calcis, the patient living only six days. The 6 recoveries occurred among patients with infections due to *Staph. haemolyticus aureus*.

The organism was recovered from the portal of entry in 31 cases before or during operation and was similar to the organism cultured from the blood. In the 4 other cases the data were as follows. Death occurred in one day in 1 case, and the organism was recovered post mortem from the portal of entry, in 1 case of prostatic abscess the organism was recovered post mortem, in the fatal case of staphylococcic endocarditis a smear could not be made ante mortem, and postmortem examination was not permitted, in 1 case of acute osteomyelitis, recovery was obtained under conservative management without operation, so that no smear could be made.

*Peripheral Blood Picture*—The picture of the peripheral blood was difficult to evaluate, as many of the patients did not live long enough for anemia to develop. For those who did survive for any length of time, repeated blood transfusions influenced the picture favorably. Therefore, anemia was not the rule. Eighteen patients showed a hemoglobin percentage between 80 and 100 per cent, 9, between 70 and 80 per cent, 7, between 60 and 70 per cent, and 1 between 50 and 60 per cent. The erythrocyte levels corresponded. The red blood cell count was between 4,000,000 and 5,000,000 in 20 cases, between 3,000,000 and 4,000,000 in 14 cases and below 3,000,000 in 1 case. In the patients with severe infection who lived longer than one week anemia occurred



and was a problem, in spite of repeated transfusions. Anemia may be expected because of two factors—the long-sustained infection, with its toxic effect on the erythroblastic function, and the hemolytic character of the organism.

The leukocyte level was of more clinical value. Leukocytosis was the rule. Seven patients showed total white blood cell counts above 30,000, 2 showed total counts below 10,000, 26 showed counts between 10,000 and 30,000 and the majority showed counts around 20,000. The 6 who recovered showed counts between 10,000 and 30,000. Too high or too low a total leukocyte count was unfavorable in this series. The polymorphonuclear neutrophil count was increased in 34 of the 35 cases as follows. In 29 it was between 80 and 100 per cent, in 5 it was between 70 and 80 per cent and in only 1 was it less than 70 per cent.

The Schilling index was obtained in only 8 cases of the series, in all of which there was a marked shift to the left, with more than 30 young forms. The degenerative index<sup>12</sup> was obtained in only 7 cases and was between 90 and 100 per cent. All of these cases were fatal.

*Urine*—The urine showed the effects of toxic parenchymatous changes in the kidneys in 25 cases by the presence of albumin, red blood cells, casts or pus. In 16 cases the urine contained acetone, denoting associated acidosis due to the severity of the infection.

*Blood Cultures*—Total colony counts were not routinely reported. In every case blood culture was positive. Each blood culture was rechecked and found to be positive on more than one occasion, with the exception of 4 cases in which death occurred in forty-eight hours or sooner. In 2 of the 4 cases a postmortem examination was made, and the organism cultured from the heart blood corresponded to the one cultured from the blood during life.

#### CLINICAL COMPLICATIONS

The complications were found by physical examination, roentgenography or laboratory study. Thirty of the 35 patients presented such complications, and 5 escaped without the detection of extension of the infection to other organs. In the majority of cases the complications consisted of the production or the development of a secondary focus of suppuration in a fixed organ or tissue. Extension of the infection or complication is the rule in this disease. Failure to demonstrate such secondary extension of the disease during life may be due to the fact that it occurs in a silent organ, defeating measures of detection and also to the fact that the grave state of the patient often prevents thorough search for foci.

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12 Mendell, T. H., Meranze, D. R., and Meranze, T. Comparative Study of Cytoplasmic and Nuclear Changes in Neutrophils in Severe Infectious States, *Am J M Sc* **192** 316-327 (Sept.) 1936.

There were no set rules as to the number or types of complications that developed, no particular sites of complications were predilected and there was no relation between the number of complications and the death rate. In general, the fewer the number of complications, the lower the mortality, yet this did not hold absolutely, as shown in cases 1 and 2, in which recovery occurred in spite of numerous complications that were almost impossible to overcome. The opposite also occurred, several patients succumbed to violent toxemia before complications could develop. The lungs and kidneys were most frequently involved in this series. This is borne out by experimental data,<sup>13</sup> which have shown that staphylococci can be injected into the blood stream of animals and within a few hours recovered from the pulmonary tissues.

Twenty-four of our patients showed pulmonary complications in the nature of septic bronchopneumonia, pulmonary abscesses, pleuritis, atelectasis or empyema. In these 24 cases the complication was secondary to osteomyelitis in 11 cases, to infections of the skin in 10 cases, to prostatic abscess in 1 case and to infection of the nasal sinuses in 2 cases. The kidneys were involved in 25 cases, as shown by abnormal urinary findings, denoting toxic parenchymatous changes, renal abscesses or carbuncles were single or multiple in 9 cases, the diagnosis being established roentgenographically, by the presence of pyuria or staphylococcuria or at operation. The renal complications were secondary to osteomyelitis in 13 instances, cutaneous lesions in 9, prostatic abscess in 1, sinus infection in 1 and pulmonary abscess in 1. The skin was secondarily involved by multiple metastatic abscesses in 10 cases, the original focus being osteomyelitis in 4, carbuncles in 3, a prostatic abscess in 2 and sinus infection in 1. The meninges and brain were involved in 7 cases, as proved by the clinical signs of meningitis and the recovery of staphylococci and pus from the spinal fluid. All were fatal. One case was due to osteomyelitis, 2 to sinus infection, 1 to carbuncle, 1 to a furuncle of the skin, 1 to a prostatic abscess and 1 to a pulmonary abscess. Toxic myocarditis occurred in 4 cases, as shown by toxic changes in the electrocardiogram. It is probable that this complication exists more frequently, because in this series electrocardiographic study was made in only 4 cases and in each of these showed changes. Secondary metastatic suppurative arthritis occurred in 4 cases, 2 being of osteomyelitic and 2 of cutaneous origin. Secondary osteomyelitis occurred in a case of primary osteomyelitis. Parenchymatous hepatitis occurred in 2 cases of cutaneous origin. Suppurative subacromial bursitis occurred as a sequela in a patient who recovered (four months after the blood culture had been sterile, case 1).

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<sup>13</sup> Wysokowitch, cited by Willetts, E. W. Blood Stream Infections, Pennsylvania M. J. **36** 312-317 (Feb.) 1933

Four patients had no demonstrable complications. One was a case of osteomyelitis of the pubic bone treated by incision and drainage, with fatal outcome and no postmortem examination. In 3 cases recovery resulted without clinical complications: a case of cellulitis of the forearm, with positive results of blood culture obtained for eight days, a case of furuncle and thrombophlebitis of the leg, with positive results of blood culture obtained for five days and a case of osteomyelitis of the pubic bone, with positive results of blood culture obtained for nine days. In the 2 last mentioned cases there were only temporary toxic urinary changes.

Definite conclusions and calculations cannot be made from these figures, because they include only demonstrable complications, without any actual data regarding the true number of complications. Nevertheless, these figures are of interest in a comparative sense. The clinical complications numbered seventy-six in 31 of the cases, making an average of two and one-half complications per case. This figure may be compared with the following postmortem data regarding complications to determine how many conditions escape clinical detection.

#### POSTMORTEM DATA

In 16 of the 29 fatal cases autopsy was performed. 7 cases of infections of the skin (four carbuncles, two abscesses and one abrasion), 6 cases of osteomyelitis, 1 case of prostatic abscess, 1 case of dental infection and 1 case of sinus infection. In all these cases the effects of the severe infection circulating in the blood stream were evident, few organs escaping pyemic invasion or toxic degenerative changes due to sepsis. In the cases in which twelve hours before death few complications or no extension of infection was evidenced, marked multiple suppurative foci were present in the viscera. There was little relation between the source of the infection and the number of organs involved. The only constant factor was the organism.

The heart showed twenty-six different lesions in the nature of cloudy swelling, muscle edema, septic vegetations on the valves, multiple myocardial abscesses, septic infarcts, suppurative pericarditis and hemo-pericardium. The majority of the cardiac complications occurred in the cases of osteomyelitic involvement.

The lungs and pulmonary structures demonstrated fifty-nine different lesions, in the nature of staphylococcic septic bronchopneumonia, bacterial septic infarcts and emboli, multiple pulmonary abscesses, fibrinous pleuritis, suppurative pleuritis, purulent bronchitis, edema, atelectasis and hemorrhage. The pulmonary complications occurred in all cases, regardless of the site of origin of the infection.

The kidneys yielded twenty-five complicating lesions, in the form of multiple abscesses (particularly cortical), bacterial emboli and septic infarcts, perineal abscesses, purulent pyelitis, cloudy swellings and hemorrhage. These also occurred in all cases.

In each of the 16 cases in which autopsy was performed, one or more lesions were present in the lungs, heart and kidneys. These organs were the site of 60 per cent of the complications.

The spleen was affected 17 times by acute splenitis or by septic infarcts and in 8 cases by abscesses. The liver was involved in 12 cases, the lesions taking the form of cloudy swelling or fatty degeneration, abscess formation was noted in 5 cases and was usually of cutaneous origin. The adrenal glands were affected by degenerative and suppurative complications in 8 cases, the pancreas in 9 cases, the gastrointestinal tract in 5 cases, the skin and dermal structures by secondary abscesses in 9 cases and bone by osteomyelitis (in 6 cases primary and in 1 case metastatic) in 7 cases. The diaphragm showed an extensive abscess in 1 case, the lymph glands showed suppurative changes in 1 case, the urinary bladder was abscessed in 1 case of prostatic abscess and in 1 case the joints were involved by suppuration. The brain was the seat of multiple abscesses in 1 case, in which meningitis complicated the course. This was the only case in which postmortem study of the brain was granted, and it is possible that this complication would have been found more frequently had the opportunity for study been given. Aside from the hepatic complications, which occurred principally in the cases of infection of cutaneous origin, and the osseous complications, which occurred only in the cases of osteomyelitis, the site of origin was of no influence with respect to the organs involved.

From these figures it will be seen that, on an average, twelve complicating lesions per case were present post mortem. It must be remembered that many of these complications existed during life in asymptomatic form or the sepsis so overwhelmed the patient that the symptoms were masked, thus defeating the diagnostic measures. However, the important point to be gathered from this postmortem study is that complications in staphylococcic septicemia are numerous, they involve most of the organs and they occur early. Failure to detect their presence clinically is in no measure a guarantee that they do not exist.

#### TREATMENT

It is difficult to evaluate any one therapeutic procedure in this disease. The gloomy outcome and the high mortality force the attending physician to utilize every possible aid which offers even the slightest hope of combating the extending infection. In the absence of specific treatment, the physician finds himself employing so many measures and remedies

that if cure does result, it is impossible to ascribe it to any one form of treatment. Then, too, the occasional occurrence of spontaneous cure adds doubt to the reputed success of certain remedies used in this disease. In many cases one form of remedy or another has been reported as successful which in the hands of other investigators has proved of no value. Yet, in spite of the meager knowledge of staphylococcic septicemia or of an effective treatment for it today, three cardinal principles for successful management stand out: (1) immediate and thorough eradication of the source of infection that is feeding the blood stream, (2) sterilization of the blood stream and (3) constant watch for the formation of metastatic foci, with prompt surgical eradication whenever possible.

*Eradication of the Source of Infection*—This means quick and adequate surgical treatment—incision and drainage, excision or amputation if necessary. This cannot be overemphasized, as it is the most important single factor in recovery of the patient. The fact that the mortality for the disease is high in spite of adequate surgical treatment in many cases, does not subtract from the value of this all-important measure. No treatment can be successful without complete removal of the focus which is feeding and reinfesting the blood stream. Surgical treatment was employed in 31 of these 35 cases. The 4 cases in which it was not employed were as follows: the case of endocarditis, the case of osteomyelitis in which the patient lived only twenty-four hours, the case of thrombophlebitis and the case of osteomyelitis of the pubic bone in which recovery followed immobilization without incision. The 3 cases which will be cited in detail illustrate how futile treatment would have been without effective surgical eradication of the source.

*Sterilization of the Blood Stream*—Today, unfortunately, there is not yet available a satisfactory disinfectant of the blood stream in staphylococcic septicemia. Until the time when there is at one's disposal as effective a remedy for staphylococcic infections as sulfanilamide has proved to be for streptococcic infections, one must rely on blood transfusions for sterilization of the blood. Repeated transfusions, preferably immunotransfusions, are of undisputed value. Transfused blood combats infection, counteracts anemia and supports the patient, the serum undoubtedly contains immunizing or neutralizing bodies effective against the staphylococcus. In 32 of the 35 cases repeated transfusions of whole blood were given, and the impression was gained that immunotransfusions were slightly superior to transfusions of citrated or of untreated blood. Of the 3 patients who were not given transfusions, 1 improved so promptly after incision into the infected area that transfusion was not necessary, 1 died in one day, before a donor could be found, and the third one had osteomyelitis of the pubic bone, with recovery by the closed method of treatment.

**Chemotherapy** Chemicals were employed liberally, only a few patients of the entire series did not receive some disinfectant. It is of great doubt whether any chemotherapeutic agent in use today can be sufficiently concentrated in the blood stream during life to prove of absolute value against the staphylococcus. Many reported recoveries have been ascribed to various chemotherapeutic agents, but on careful review of these cases so many other factors are found to have entered into the treatment that the effectiveness of the germicide in itself cannot be gaged. In this series gentian violet was used in 16 cases, Pregl's iodine solution in 8, neoarsphenamine in 3, mercurochrome in 2, metaphen in 1, acriflavine in 1 and sulfanilamide in 3. Sulfanilamide not only did no good in these cases but in 1 case caused hepatitis with jaundice of alarming degree, which disappeared after its discontinuation.

**Biologic Agents** (a) **Bacteriophage** No discussion of staphylococcic septicemia would be complete without mention of bacteriophage. It was employed in 12 of these cases—in 2 cases locally and in 2 cases subcutaneously. These 4 cases were fatal. In the 8 other cases it was used intravenously, according to the technic of MacNeal and Frisbee,<sup>10</sup> with unsuccessful results. Death resulted in 6 cases. In the 2 nonfatal cases, bacteriophage had no effect at all in 1, and in the other it was definitely shocking and harmful and produced no effect on the blood culture. Its use was abandoned in each case after two courses, while the patient was still in a critical condition, the eventual recovery was in no way influenced by the administration of bacteriophage.

(b) **Staphylococcus antitoxin** This was used in 3 cases, with 2 recoveries, but these could not be credited to the antitoxin. With so many strains of staphylococci, it is not likely that a polyvalent antitoxin covering the many groups would contain sufficient units of antitoxin specific for the offending strain attacking the patient to be of any decided value. Indeed, it is doubtful if the offending strain is present in the stock antitoxin in any given case. Such exquisite pain is caused by the intramuscular administration of the antitoxin that one wonders if it is worth the inconvenience and the loss of sleep imposed on the patient. However, in the future there is a possibility that this method of approach to the problem may be of paramount value when individual strains of staphylococci can be isolated and effectively neutralized and specific antitoxins obtained.

(c) **Staphylococcus toxoid** This was used in 2 cases, 1 case was fatal, and in the other the toxoid was given after recovery had been established, so that its usefulness could not be appraised in this study.

**Miscellaneous Forms of Treatment** Roentgen therapy was used in 2 cases and foreign protein therapy in 1 case. The results were questionable.

*Constant Watch for Metastatic Foci, with Prompt Eradication by Surgical Treatment Whenever Possible*—The blood stream may be sterilized, and yet if the state of sepsis is continued by a metastatic focus, the blood stream may be reinfected. Of course, metastatic foci are not always accessible, therefore it is not possible to eradicate them in every case (multiple pulmonary abscesses in case 1). In such instances supportive measures offer the only hope. Case 2 shows how effectively bilateral renal abscesses were combated by surgical measures and that recovery would have been impossible in this case without their removal. No amount of surgical treatment is too much until all accessible foci are removed.

#### PROGNOSIS

From this study and other reported studies of staphylococcic septicemia, the following factors are found to bear on the prognosis of this desperate infection. The possibility of eradicating the primary focus of infection that is feeding the blood stream as well as the possibility of combating the extension of the infection into distant organs and removing metastatic foci influences the prognosis favorably. The sthenic age, young adulthood, as in most diseases, is the most favorable age with respect to combating the disease. Most of the recoveries in this series occurred in this age group. The promptness with which treatment is instituted is important for a favorable outcome. In many cases the disease is not recognized early enough so that measures can be taken to prevent its deadly effects and extension. It is not uncommon for the condition to be treated under a mistaken diagnosis for some time before the true state of affairs is recognized. Pneumonia was the most frequently mistaken diagnosis in this series and the error can readily be understood when chill, fever and cyanosis and often rales in the chest, with leukocytosis, all of sudden onset, confront the examiner. Lagrippe was a frequent mistaken diagnosis in the cases of osteomyelitis. If the disease can be recognized at the onset and surgical treatment, transfusions and other measures employed to prevent extension, the chances of recovery are greatly enhanced.

Positivity of the result of blood culture is also a factor in the prognosis. The less numerous the colonies of staphylococci in the blood culture, the more favorable the chances for recovery.

The coexistence of other disease states, particularly diabetes mellitus, with staphylococcic septicemia offers a very poor outcome. There were 9 such cases and all were fatal. The extension of the disease to the brain, meninges or heart likewise influences the prognosis unfavorably. The 7 patients with meningitis and the 4 with cardiac toxic changes all died. The very young and the aged do poorly with this infection. The impossibility of eliminating the original source of infection or of prohibiting the extension of the infection also influences the prognosis unfavorably. Delay in treatment may also cost a life.

## REPORT OF THREE CASES IN WHICH RECOVERY WAS OBTAINED

CASE 1—D M, a man aged 33, was admitted to the Mount Sinai Hospital under the author's care on June 10, 1937, because of a sudden chill and elevation of the temperature to 103 F, secondary to a huge carbuncle on the back. He was toxic, septic and acidotic, the leukocyte count was high and the urine was loaded with casts, albumin, red blood cells, white blood cells and acetone. One hour after entry the carbuncle was decapitated and drained (by Dr Benjamin Lipshutz), the organism obtained was *Staph aureus haemolyticus*. A twenty-four hour blood culture showed *Staph aureus haemolyticus*. Repeated daily incisions into the carbuncle for wider drainage, several transfusions, staphylococcus antitoxin and supportive measures failed to halt the advancing infection and downhill course. The results of blood culture increased in positivity, and the general condition was critical. At this point, on June 14, a wide excision of the entire carbuncle and surrounding area into healthy tissue was performed, leaving an open wound down to the ribs measuring 7 by 8 inches (18 by 20 cm). This seemed to be the only means of removing the source of infection that was feeding the blood stream. A specific bacteriophage was then ready and was used locally and intravenously, after the method of MacNeal and Frisbee. After the sixth injection intravenously, the patient had a violent chill, with rigor, and the temperature reached 106.4 F, followed by vasomotor collapse and shock of alarming degree, with a drop in temperature to 100 F and a rise to 104 F in the afternoon. Blood culture the following day showed no change, and the general condition of the patient was poorer. On June 18 signs of involvement of the lower lobe of the right lung were present. The next day bacteriophage therapy was repeated, and after the fifth dose intravenously the shock and collapse reaction were so violent and the effects so weakening, without any measure of improvement clinically or in the state of the bacteremia, that this form of treatment was abandoned. On June 19 empyema of the right side of the chest was discovered and tapped, 150 cc of purulent fluid was obtained, which yielded *Staph aureus haemolyticus*. A roentgenogram of the chest showed pleurisy over the lower lobe of the right lung associated with atelectasis, pneumonitis of the left lung and small areas of consolidation scattered throughout both pulmonary fields. Repeated roentgen examinations of the chest soon disclosed, in addition to these findings, the development of five large metastatic abscesses in the lungs. Sulfanilamide therapy was tried but was discontinued because of the development of hepatitis and jaundice. With repeated immunotransfusions, the administration of gentian violet intravenously and Pregl's iodine solution, supportive measures, and incision and drainage of metastatic abscesses of the skin as they occurred, the clinical condition showed some improvement, and on July 11, thirty-two days after entry, blood culture became sterile for the first time. The sepsis continued, however, owing to the many metastatic foci of suppuration, particularly in the lungs. The temperature ranged from 101 to 104 F daily. On July 31 the patient experienced sudden pain in the right loin and voided 10 ounces (300 cc) of nearly pure pus, which yielded *Staph aureus haemolyticus*. Undoubtedly, spontaneous rupture of a renal carbuncle into the renal pelvis and discharge through the urinary tract occurred. In a few days the urine was clear, with no pus or organisms. Gradually the pulmonary complications improved, and on August 10 roentgen examination revealed disappearance of the pneumonitis, improvement in the atelectasis and beginning resolution of the five abscesses. On September 10 the temperature was normal for the first time, the patient was asymptomatic and the pulmonary condition was better. On September 26 the patient was discharged improved (afebrile) and had



regained 20 of the 50 pounds (9 of the 227 Kg) which he had lost during his illness. For six weeks he was convalescing at home and doing well, with a gain in weight, when sudden severe pain in the left shoulder and disability of motion, with chills and fever developed. He was readmitted to the hospital on November 16 in a toxic condition. Blood culture was sterile. Surgical drainage (by Dr M. B. Cooperman) of an acute suppurative subacromial bursitis on the left side yielded *Staph aureus haemolyticus* (more than four months after the blood had been sterile). Uneventful recovery followed. He is well and asymptomatic and is working full time today. His weight is greater than it has been at any period of his life.

*Comment*—Treatment consisted of effective surgical eradication of the source of infection, removal of metastases when possible, thirteen blood transfusions, of which eleven were immunotransfusions, chemotherapy, and the administration of staphylococcus antitoxin and bacteriophage.

CASE 2—A. DeM., a 23 year old man, was admitted to the service of Dr. A. I. Rubenstone on March 16, 1937, in a septic, toxic state, suffering from a gluteal abscess of one week's duration. The temperature ranged between 101 and 104 F. The abscess was opened and drained, and the pus yielded *Staph aureus haemolyticus*. The blood culture made on entry showed in forty-eight hours *Staph aureus haemolyticus*. Roentgen treatment over the abscess, repeated transfusions, gentian violet, Pregl's iodine given intravenously and staphylococcus antitoxin produced no response. The condition was grave. Pulmonary extension was detected clinically. Metastatic abscesses appeared on the toe and shoulder and on incision yielded *Staph aureus haemolyticus*. On April 1 a specific bacteriophage was given intravenously, according to the method of MacNeal and Frisbee, with no effect. Thirty-one days after entry, with transfusions given every other day, blood culture became sterile for one week, although sepsis continued, finally, on May 2, the blood became sterile and remained so. Another course of treatment with specific bacteriophage was given, with no reaction. In spite of the sterile condition of the blood stream, sepsis, leukocytosis and anemia continued. Toxic hepatosplenomegaly with jaundice continued for weeks. The condition remained stationary until July 22, when the search for metastatic foci of suppuration was rewarded by definite urographic evidence of a huge abscess of the left kidney. Pyuria, with the recovery of staphylococci from the urine, caused suspicion of the renal condition. Nephrectomy was performed by Dr. M. Muschat, the removed kidney contained two large abscesses in the upper and middle portions, from which *Staph aureus haemolyticus* was obtained. The temperature and pyuria disappeared for three weeks, during which time there was remarkable clinical improvement. However, fever and pyuria recurred, and on August 20 a urogram showed a huge abscess in the other kidney. Conservative treatment was elected, but because of increasing sepsis and the downhill clinical course, exploration of the remaining kidney was done on September 8. The perinephric tissues were edematous and adherent and a large abscess in the lower pole was incised and drained, as well as one in the middle pole. Both yielded *Staph aureus haemolyticus*. The patient did well immediately after operation, the temperature soon reached normal and he gained strength and weight and soon became asymptomatic. He was discharged on October 3. He is now well and back at work.

*Comment*—Treatment consisted of surgical eradication of the focus of origin, effective eradication of the metastatic foci of suppuration, without which life would have been impossible, twenty-four blood transfusions, the administration of staphylococcus antitoxin and bacteriophage, chemotherapy, and irradiation

CASE 3—M G, a 13 year old boy, was admitted to the service of Dr A Trasoff on May 1, 1937, because of cough, chill, fever and signs of pneumonic consolidation of the lower lobe of the left lung. The temperature was 105 F, toxicity was marked, a toxic rash covered the body, the leukocyte count was high and the urine was loaded with casts and acetone. There was a fluctuating tender swelling of the right shoulder of two days' duration. Blood culture in twenty-four hours showed *Staph aureus haemolyticus*. A roentgenogram did not show acute osteomyelitis of the humerus, but the clinical diagnosis was evident. The high temperature persisted, being sustained at 105 F. Accordingly, incision and drainage of the humerus were performed by Dr M B Cooperman, and pus was obtained which yielded *Staph aureus haemolyticus*. After surgical drainage the blood culture became sterile within three days, or five days after entry. Within ten days the patient was afebrile. One metastatic abscess of the skin occurred which promptly responded to incision. The patient was discharged cured twenty-four days after entry.

*Comment*—Treatment consisted of surgical eradication of the focus that was feeding the blood stream (this controlled the septicemia), two blood transfusions and the administration of staphylococcus antitoxin and gentian violet intravenously.

#### SUMMARY

Staphylococcic septicemia is the most deadly of all septicemias. A series of 35 patients, seen over an eight year period, is presented. There were 6 recoveries, 29 fatalities and 16 postmortem examinations. The mortality was 83 per cent, which compares well with the rates reported in the literature.

The incidence, sex, age, source of infection, duration of the disease, laboratory findings, complications noted clinically, as contrasted with complications noted post mortem, treatment, and prognosis are discussed. It is shown that complications occur early in the course of the disease and exist more frequently than can be discovered clinically.

In the light of present knowledge of the disease, with no specific treatment as yet available, surgical eradication of the source of infection, with prompt removal of metastatic foci of suppuration as they occur, plus repeated immunotransfusions, offers the foundation for any successful treatment. Three cases in which recovery was obtained are discussed in detail to emphasize these features of the disease.

# CORTICAL NECROSIS OF THE KIDNEY FOLLOWING TONSILLITIS

REPORT OF A CASE

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Bilateral, symmetric necrosis of the renal cortex is a rare condition which during the life of the patient often represents a rather difficult diagnostic problem. Kaufmann<sup>1</sup> described this condition as an extensive necrosis of the cortex of the kidney leading to rapid suppression of the excretion of urine and to death attended by uremic symptoms. Extensive confluent yellowish areas of cortical necrosis are found surrounded by deep red hemorrhagic rims and associated with extensive thromboses of the intrarenal arteries and veins. This lesion has been observed chiefly as a fatal complication of pregnancy, and 86 per cent of the cases reported in the literature fall in this group (Evans and Gilbert<sup>2</sup>). Other etiologic factors, such as tonsillitis, periaarteritis nodosa, diphtheria, pulmonary tuberculosis, peritonitis and intravenous injections of camphor, must be considered as extremely rare, they are responsible for the small number of cases in which the condition has occurred in males. Because of the rarity of the condition and the interesting etiologic background, we wish to report briefly the following case.

## REPORT OF CASE

A white boy 17 years of age entered the University Hospital on Jan 10, 1938, with pain and tenderness in the lumbar region and swelling of the feet and ankles, face and right forearm. This condition had developed slowly after a prolonged attack of tonsillitis one month previously. The history was negative with regard to previous diseases, and the patient had been in perfect health until the time of the initial illness.

*Examination*—The patient was rather emaciated but did not appear acutely ill. The tonsils were small and contained deep crypts. The blood pressure was 130

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systolic and 80 diastolic. The heart was moderately enlarged to the left, and a soft systolic murmur was present over the apex. There was muscular tenderness over both kidneys, but no edema of the feet or ankles could be observed during the patient's stay in the hospital. Examination of the urine showed a specific gravity of 1.020 and an albumin content of 300 mg, in the microscopic examination of the sediment about 70 red blood cells and 30 white blood cells could be observed per high power field, with numerous granular and cellular casts. Examination of the blood showed 2,040,000 red cells and a hemoglobin content of 50 per cent. The leukocyte count was 35,000, with 68 per cent neutrophilic leukocytes and 17 per cent juvenile leukocytes. The platelet count was 607,700, and there were 4 per cent reticulocytes. The renal function test with phenolsulfonphthalein revealed an excretion of only 55 per cent of the dye in three hours. The concentration-dilution test showed moderate disturbance of renal function. The blood urea clearance at the time of the patient's admission was 48.19 per cent. The albumin-globulin ratio of the blood serum was 3.2:3.3. The blood cholesterol was 153.8 mg per hundred cubic centimeters. Cultures of the blood were negative. The electrocardiographic examination showed a slight defect of the intraventricular conduction. The roentgen examination of the chest showed a diffuse dense area in each pulmonary field, which was interpreted as indicating possible pneumonic infiltration or severe passive congestion. The serologic tests for syphilis were negative. At admission there was marked oliguria, which lasted for three days but disappeared suddenly.

*Course*—With rest, an antinephritic diet and general supportive treatment the patient improved greatly. The nonprotein nitrogen level of the blood sank from 60 mg per hundred cubic centimeters to 30 mg. The patient was discharged on the thirty-fourth hospital day.

One week after having been discharged the patient was seized by an attack of acute dyspnea and hemoptysis and he was readmitted to the hospital on March 4. At this time the blood pressure was 160 systolic and 130 diastolic. Coarse rales were audible over both lungs. The heart showed a gallop rhythm and a blowing first sound at the apex. There was tenderness over both kidneys. There was slight pitting edema over the ankles and sacrum. Examination of the urine showed a specific gravity of 1.023 and 200 mg of albumin. The reaction for Bence Jones protein was strongly positive. The microscopic examination of the sediment showed 8 red blood cells and 12 white blood cells per high power field with numerous hyaline and erythrocyte casts. The examination of the blood showed an erythrocyte count of 2,950,000 and a hemoglobin content of 50 per cent. The white blood cells numbered 45,640, with 74 per cent neutrophilic leukocytes and 6 per cent juvenile forms. The phenolsulfonphthalein test for renal function revealed an excretion of only 35 per cent of the dye in two hours, and a concentration test showed definitely disturbed renal function. An intravenous pyelogram showed anatomically normal kidneys. The sedimentation rate of the red blood cells was greatly increased. The electrocardiographic examination showed definite evidence of myocardial damage. The patient was placed again on a high protein and salt-free diet with supportive treatment and restriction of fluids. His temperature showed moderate elevation. The output of urine suddenly became markedly decreased, the patient started to vomit, diarrhea developed, and he became somnolent. Examination of his eyegrounds showed the presence of retinal hemorrhages. Two days before death he had complete anuria and brief attacks of convulsions, followed by deep coma. He died on the eighteenth day in the hospital.

*Autopsy*—The body was well developed but poorly nourished. Scattered over the face were numerous purplish spots, 1 to 3 mm in diameter. The back and the tip of the nose showed purplish discoloration. The skin and mucous membranes appeared slightly anemic. The hands, the forearms, the lower parts of the legs and the feet showed a moderate degree of pitting edema. The nails were deeply evanotic. There were scattered purplish spots over the left forearm. Larger areas of subcutaneous hemorrhage were present over the thighs.

The heart weighed 450 Gm. The left ventricle showed hypertrophy and moderate dilatation. The pericardium and myocardium showed no pathologic changes. The endocardium showed a few antemortem thrombi located between and behind the trabeculae of the ventricles. An antemortem thrombus was also observed in the left auricular appendage. Both lungs were voluminous and well expanded. The pleura presented many confluent and discrete petechial hemorrhages. The lung tissue showed numerous moderate-sized, recent hemorrhagic infarcts. There also were considerable edema and passive congestion in the lower lobes. The spleen weighed 200 Gm and was soft. There was a diffuse increase in the pulp substance. The liver weighed 1,600 Gm. Irregular congestion was present, which gave the organ a reddish brown mottled appearance. The esophagus contained blackish material, which also stained its wall. The mucous membrane of the stomach showed numerous ecchymoses and some irregular areas of atrophy. The ileum and the colon showed circumscribed areas of congestion. The kidneys were enlarged and weighed 210 Gm each. The capsules stripped with some difficulty. The surface of the kidney showed irregular mottling, with confluent areas of yellowish gray most prominent. Some of these areas were surrounded by deep reddish lines of demarcation, while others seemed to be surrounded by small zones of normal kidney tissue. The cut surfaces of the kidneys revealed a marked yellowish red mottling of the cortical zone, with the yellowish areas by far in predominance. The medullary tissue appeared normal except for some hemorrhagic streaks in the subcortical regions. The mucous membrane of the kidney pelvis and the ureters were normal. The urinary bladder was well contracted and contained a few cubic centimeters of cloudy urine. One testicle showed a large diffuse parenchymatous hemorrhage. Section of the brain revealed petechial hemorrhages in the region of the thalamus and in the choroid plexus of the lateral ventricles.

Microscopic examination of the heart revealed moderate hypertrophy of the heart muscle. Some of the muscle fibers showed marked fatty degeneration. A few of the smaller coronary vessels were dilated, their lumens filled with thrombotic material containing polymorphonuclear leukocytes, erythrocytes and an amorphous granular material. Sections of the lungs showed large areas of hemorrhagic infarction surrounded by zones of pneumonic infiltration. The pulmonary vessels appeared dilated. Some of them showed hyalinization of the wall, while others were filled with small thrombi. In the infarcted areas large colonies of cocci could be recognized. The spleen showed moderate hyperplasia of the pulp with an increase of polymorphonuclear leukocytes. A few small splenic arteries showed partial hyalinization of the walls with thrombus formation. Sections through the lymph nodes showed marked congestion of vessels and increased desquamation of the endothelium of the sinuses. The liver showed moderate parenchymatous degeneration of the hepatic cells. The dark reddish areas of liver tissue showed marked acute congestion with destruction of the center of the hepatic lobule. The brownish parts of the liver showed no congestion of the capillaries and only moderate fatty degeneration in the center of the hepatic lobule.

The vessels of the liver did not show any pathologic changes. Sections of the esophagus showed extensive superficial necrosis of the mucous membrane with phlegmonous infiltration of the submucous layer and hemorrhagic imbibition of the necrotic area. Some of the vessels in the submucous region appeared to be thrombosed. The adrenal gland showed lipoid depletion of the cortex, moderate passive congestion, an occasional small focus of necrosis and minute areas of hemorrhage. Sections of the skin and the subcutaneous tissue showed small petechial hemorrhages. Sections of the brain showed numerous thrombi in the



Fig. 1—Cut surface of the kidney, showing the gray areas of cortical necrosis

smaller vessels with extravasation of blood into the perivascular lymph spaces. The thrombi were principally hyaline and amorphous in nature. The wall of the vessel seemed sometimes to be infiltrated with leukocytes.

Sections of the kidneys showed a change resembling a diffuse and irregular infarction of the entire cortical zone. Some glomeruli were enlarged and filled with blood, others were small and necrotic. Occasionally some fibrosis of the capsule could be observed, indicating previous glomerular damage. The afferent vessels were greatly dilated and showed hyalinized thrombi, which in some cases continued into the loops of the glomerular capillaries. The walls of the afferent

capillaries were often hyalinized or necrotic. A few noninfarcted glomeruli showed an increase in cells suggestive of a proliferative type of glomerular nephritis, while others were normal. The tubular epithelium showed extensive



Fig. 2—Coagulation necrosis of the cortex of the kidney surrounded by a wall of leukocytes, hematoxylin and eosin stain,  $\times 120$

necrosis with marked desquamation and an amorphous pink-staining material filling the lumens. The interlobular arteries and veins were greatly dilated and showed partial or complete hyalinization of the walls. The lumen was filled with thrombi consisting of an amorphous granular material, red blood cells and

leukocytes The arterial thrombi were predominantly hyaline or amorphous in character, while the venous thrombi were more cellular Diffuse imbibition of the thrombus as well as of parts of the vascular wall with fibrosis could be demonstrated with the method of Weigert With Unna's stain a large amount of



Fig 3—Thrombus formation in the interlobular vessels, hematoxylin and eosin stain,  $\times 120$

hyalin could be demonstrated in the thrombi of the afferent vessels and in the loops of the glomeruli The interstitial tissue of the kidney appeared edematous and slightly infiltrated with leukocytes and round cells There was a dense zone



of leukocytes just beneath the capsule forming a line of demarcation around the infarcted tissue. The medulla showed moderate congestion of blood vessels but no evidence of tissue necrosis.

## COMMENT

Cortical necrosis of the kidney is clinically characterized by its rapid and relatively symptomless course (Davidson and Turner,<sup>3</sup> Torrens<sup>4</sup>). Its most important symptoms are nocturia, oliguria and, finally anuria (Manley and Klman<sup>5</sup>). The last is without doubt the most striking feature of the disease, although it is not complete in most cases (Rolleston,<sup>6</sup> Wordley<sup>7</sup>). Convulsions, headache, impaired vision, edema and diarrhea may be regarded as terminal symptoms indicating an advanced stage of uremia (Ash<sup>8</sup>). In the case of Bradford and Lawrence<sup>9</sup> the patient remained lucid until his death. Pain and tenderness in the region of the kidneys were mentioned by Manley and Klman,<sup>5</sup> while in the cases of Bamforth<sup>10</sup> and von Zalka<sup>11</sup> abdominal pain preceded the anuria. The small quantity of urine excreted contains a large amount of albumin, red blood cells and leukocytes, with numerous granular and hyaline casts. The appearance of Bence Jones protein in our case must be recorded as unusual. The leukocyte count of the blood is usually greatly elevated (Manley and Klman<sup>5</sup>), in our case the number of white cells rose to 46,000. The blood pressure is variable ranging from normal levels to a systolic high of 200 mm of mercury (Evans and Gilbert<sup>2</sup>). The temperature may be elevated, especially in the presence of bacterial infection, but it often becomes subnormal in the later stages.

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of the disease (Apert and Bach<sup>12</sup>) Chemical studies of the blood reveal in all cases a rapid rise in the retention of nitrogenous products, which can often be demonstrated in hourly intervals (Dalrymple<sup>13</sup>) Retinal edema (Hirst<sup>14</sup>) or a cotton wool appearance of the disks (Carson and Rockwood<sup>15</sup>) is present in a large number of cases, often associated with capillary hemorrhages, as we observed The duration of the disease depends on the degree of suppression of urination If it is complete, death may be observed as early as twenty-four hours after its onset (Torrens<sup>4</sup>), while in cases of incomplete anuria a duration of from fourteen to twenty-one days has been observed Gibberd<sup>16</sup> published reports of 2 cases in which the patient recovered from anuria lasting nine and ten days, respectively, the nonprotein nitrogen level of the blood returning to normal a few days after cessation of the anuria In such cases the diagnosis of cortical necrosis was disputed by Scriver and Oertel,<sup>17</sup> who expressed the belief that the mere fact of recovery speaks against the presence of this renal lesion Death usually occurs after the sudden appearance of severe uremic symptoms, accompanied by coma and convulsive seizures

At autopsy the kidneys usually are slightly enlarged, with a mottled yellowish gray and dark red or violet red surface (Juhel-Rénoy<sup>18</sup>) The greater part of the cortex shows a whitish yellow color characteristic of ischemic necrosis and is surrounded by thin dark red serrated lines of demarcation (Glynn and Briggs<sup>19</sup>) The renal pyramids are usually dark red and of normal texture Subcapsular hemorrhages have been described by Jardine and Teacher<sup>20</sup> Grossly recognizable throm-

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19 Glynn, E E, and Briggs, M B Symmetrical Cortical Necrosis of the Kidney in Pregnancy, *J Path & Bact* **19** 321-332, 1915

20 Jardine, R, and Teacher, J H Two Cases of Symmetrical Necrosis of the Cortex of the Kidneys Associated with Puerperal Eclampsia and Suppression of Urine, *J Path & Bact* **15** 137-146, 1910

bosis of the larger renal vessels was present in the case of Rolleston.<sup>10</sup> In the microscopic examination the characteristic changes are confined to the cortical zone and are remarkable for their uniformity. The lesion resembles an anemic infarct except for its irregular outline and the marked engorgement of the vessels in the necrotic area (Ash<sup>8</sup>). A small strip of subcapsular cortical tissue is often intact and separated from the necrotic area by dense zones of leukocytes (Bamforth<sup>10</sup>). Similar zones of nonnecrotic tissue, often filled with small hemorrhages, may be observed just above the medulla. In our case the necrotic areas had a distinctly confluent character, and small islands of non-necrotic kidney tissue could be seen between the areas of infarction. The wall of leukocytes demarcating the necrotic tissue was absent in some places. The glomerular changes in this condition may be manifold. Some glomeruli show hemorrhagic infarction, while others appear collapsed and necrotic. Hyaline thrombi could be observed by us in some afferent vessels while Juhel-Renoy<sup>18</sup> and Hirst<sup>11</sup> reported the occurrence of fibrin thrombi in the loops of the glomeruli. Evidence of chronic glomerular nephritis was present in the case of Glynn and Briggs,<sup>19</sup> and also in our case glomeruli not involved in the necrotic process showed some endothelial proliferation with fibrosis. The presence of eosinophilic cells in the tufts was mentioned by zu Jeddelloh,<sup>21</sup> an increase of intravascular fat in the glomerular tufts was described by Warner and Hibbitts,<sup>22</sup> and the presence of microbes in the glomerular loops was stressed by Juhel-Renoy. The tubular epithelium in the necrotic cortical areas shows all degrees of cloudy swelling, fatty degeneration and coagulation necrosis. The outline of the structure of the tubules is usually preserved. The lumen may be dilated and filled with amorphous casts containing large amounts of fibrin (zu Jeddelloh<sup>21</sup>). The tubular epithelium in the capsular zone has a marked tendency to cloudy swelling (Bradford and Lawrence<sup>9</sup>). The collecting tubules in the medulla may show slight degenerative changes, the lumen containing albuminous casts. The lack of necrosis was explained by Scriver and Oertel<sup>17</sup> by an increased anastomosis of the vessels therein. The most striking feature of the lesion is without doubt the appearance of massive thrombi in the vessels of the cortical zone. The interlobular arteries and veins as well as their branches are plugged by thrombotic material consisting of amorphous material, leukocytes and erythrocytes. In our case the venous thrombi were more cellular, while the arteries were usually filled with homogeneous hyaline material. The presence of a large amount of platelets in these thrombi

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21 zu Jeddelloh, B. Eine seltene Form akuter tödlicher Nierenerkrankung nach Fehlgeburt, *Virchows Arch f path Anat* **286** 389-408, 1932.

22 Warner, C. G., and Hibbitts, J. T. Symmetrical Cortical Necrosis of the Kidneys in Pregnancy, *Am J Obst & Gynec* **23** 875-881 1932.

was described by Manley and Kliman<sup>5</sup> The wall of the vessel usually takes on a hyaline, or even necrotic, appearance (zu Jeddeloh<sup>21</sup>), and sometimes endarteritis is present, which, however, is not the most impressive part of the pathologic picture (Lloyd<sup>23</sup>) In some places the elastic fibers of the vessels are completely destroyed, and small hemorrhages can be seen in the perivascular zones

In Bell's<sup>24</sup> excellent discussion of clinical acute nephritis, two groups of lesions are listed which must be differentiated from widespread primary thrombosis of small renal arteries Both represent subtypes of acute glomerular nephritis, namely, the type associated with thrombosis of glomerular capillaries and the type associated with thrombosis of afferent arterioles In none of these types, however, will actual tissue necrosis involving large areas of cortical zones occur, nor is the presence of thrombotic masses of the larger vessels observed

The cause of the thrombosis of the renal vessels is still under dispute Since damage to the endothelium by toxins is one of the commonest causes of thrombosis (Glynn and Briggs<sup>19</sup>), such injury to the vessels could well be expostulated as the primary factor in this lesion The theory of Juhel-Rénoy that organisms may be the primary cause of plugging of the lumen of the vessel with secondary thrombus formation can be regarded as obsolete The histologic examination in our case seemed to support well the theory of primary damage to the wall of the vessel as the cause of thrombus formation since similar changes were observed also in the spleen, lung, heart and brain, leading to thrombosis with infarction of the lung and encephalomalacia The predominant involvement of the renal vessels in the thrombotic process may be partly explained in our case by increased blood stasis in the interlobular arteries caused by the existing glomerular damage

There is also considerable dispute as to the importance of these thrombi in the causation of the cortical necrosis De Navasquez<sup>25</sup> expressed the belief that thrombosis is conspicuous for its extreme infrequency, and that it is only a terminal symptom, representing aggregated masses of blood cells consequent to stasis In 14 of 44 cases collected by Ash<sup>8</sup> no thrombi were reported Also, Dalrymple<sup>13</sup> stated that the thrombosis in the vessel is secondary to necrosis Against this argument we may cite again the observations made in our case, in which thrombi associated with changes in the vascular walls caused infarction in the lungs and the brain, while they were observed without tissue

23 Lloyd, H C Necrosis of the Entire Renal Cortex of Both Kidneys, *Lancet* **1** 156, 1906

24 Bell, E T The Early Stages of Glomerulonephritis, *Am J Path* **12**, 801-824, 1936

25 De Navasquez, S The Histology and Pathogenesis of Bilateral Cortical Necrosis of the Kidney in Pregnancy, *J Path & Bact* **41** 385-396, 1935

necrosis in the spleen and the heart. They cannot be regarded, therefore, as sequelae of the tissue necrosis.

With regard to the angiospastic theory of Ash<sup>8</sup> and Schmorl and Beneke,<sup>26</sup> we may emphasize that the marked dilatation of the obstructed vessels rather should suggest toxic vasoparalysis, as assumed by Scriver and Oertel. This again, would be an additional factor in promoting thrombus formation.

#### SUMMARY

A case of symmetric cortical necrosis of the kidneys following tonsillitis is reported. The microscopic picture revealed evidence of existing glomerulonephritis on which the ischemic necrotic process was superimposed. The interlobular arteries and veins and their smaller branches showed hyalinization of the wall with thrombus formation. Similar, but less marked, changes could be observed also in the vessels of the spleen, heart, lungs and brain. The importance of damage to the wall of the vessel by circulating toxins in production of the thrombi with subsequent tissue infarction is discussed.

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26 Schmorl and Beneke, cited by Kaufmann<sup>1</sup>

# EXCRETION OF ASCORBIC ACID IN RELATION TO SATURATION AND UTILIZATION

WITH SOME DIAGNOSTIC IMPLICATIONS

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In the past few years numerous reports have appeared in the literature dealing with the metabolism of ascorbic acid in man. These studies made use of the Harris-Ray<sup>1</sup> modification of the Tillman method of titrating for this substance in the urine and the Farmer-Abt<sup>2</sup> method for its detection in blood plasma. Several general conceptions were evolved from these studies:

1 Ascorbic acid is excreted in the urine in its reduced state in almost all persons, the exact quantity depending on the amount of intake, but the minimal normal amount is considered to be around 20 mg per twenty-four hours<sup>3</sup>

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1 Birch, T W, Harris, L J, and Ray, S N. A Micro-Chemical Method for Determining the Hexuronic Acid (Vitamin C) Content of Foodstuffs, etc., *Biochem J* **27** 590, 1933

2 Farmer, C J, and Abt, A F. Ascorbic Acid Content of Blood, *Proc Soc Exper Biol & Med* **32** 1625, 1935

3 (a) Youmans, J B, Corlette, M B, Akeroid, J H, and Frank, H. Studies of Vitamin C Excretion and Saturation, *Am J M Sc* **191** 319, 1936, (b) A Clinical Study of Vitamin C Excretion, *South M J* **29** 37, 1936 (c) Drigalski, W V. Ueber Vitamin C im Urin von Gesunden und Kranken, *Klin Wchnschr* **14** 338, 1935 (d) Hawley, E E, Stephens, D J, and Anderson, G. The Excretion of Vitamin C in Normal Individuals Following a Comparable Quantitative Administration in the Form of Orange Juice and Cevitamic Acid by Mouth and Cevitamic Acid Intravenously, *J Nutrition* **1** 135, 1936 (e) Schroeder H. Ueber die Ausscheidung der Ascorbinsäure in gesunden und kranken Organismus, *Klin Wchnschr* **14** 484, 1935 (f) Finkle, P. Vitamin C Saturation Levels in the Body in Normal Subjects and in Various Pathological Conditions, *J Clin Investigation* **16** 587, 1937 (g) Van Eekelen, M, Emmerie, A, Josephy, B, and Wolf, L K. Ueber Vitamin C in Körperflüssigkeit, *Klin Wchnschr* **13** 564, 1934 (h) Harris, L J, and Ray, S N. Diagnosis of Vitamin C Subnutrition by Urine Analysis, *Lancet* **1** 71, 1935 (i) Harris, L J, Ray, S N, and Ward, A. The Excretion of Vitamin C in Human Urine and Its Dependence on Dietary Intake, *Biochem J* **27** 2011, 1933 (j) Johnson, S N, and Silva, S S. The Urinary Excretion of Ascorbic and Dehydroascorbic Acid in Man, *ibid* **28** 1393, 1934

2 Reduced ascorbic acid is found in the blood stream of normally nourished persons, the concentration of this is 0.7 to 0.9 mg per hundred cubic centimeters of plasma or higher.<sup>1</sup>

3 Ascorbic acid is stored in almost all of the tissues of the body, and when these body stores are filled to capacity the state has been referred to as "saturation."

Thus, if a person excretes much less than 20 mg per twenty-four hours, it has been regarded as a sign of a deficient intake of the vitamin, but the degree of deficiency cannot be surmised from this alone. The concentration in the blood if it is in the very low levels or the very high levels is a fairly good index of the immediate state of vitamin C nutrition, but if it is in the borderline levels it is more uncertain. In this respect the "saturation test" is much more helpful. If a fairly large dose consisting of several hundred milligrams of ascorbic acid, is administered to a normal person, a sharp rise in the amount excreted in the urine occurs within several hours,<sup>6</sup> and in twenty-four hours normal persons will have excreted 30 per cent or more of a 600 mg test dose.<sup>7ab</sup> If such a large dose is given to a person who is deficient in the vitamin, no rise in the amount excreted will take place until the body stores are beginning to be filled, and this will take longer if the body stores are more completely depleted. It has also been demonstrated that normal persons will excrete 75 per cent or more of this intake when the body stores have been completely filled or saturated,<sup>3a, b, c</sup> although unexplained fluctuations have been noted.<sup>6a</sup> Another test<sup>7</sup> for vitamin C saturation proposed consists of administering intravenously 100 mg of ascorbic acid and examining the postinjection urinary excretion of the vitamin.

It is generally assumed that low urinary excretion and low blood concentration of ascorbic acid is indicative of a deficient intake. However, it has been demonstrated that at least in febrile patients there is a decreased excretion of ascorbic acid which is not wholly dependent on

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4 (a) Greenberg, L. D., Rimelant, I. J., and Phatak, N. M. Studies on Reduced Ascorbic Acid Content of Blood Plasma, *Proc Soc Exper Biol & Med* **35** 135, 1936. (b) Taylor, F. H. L., Chase, D., and Faulkner, J. M. Estimation of Reduced Cevitamic Acid in Blood, Serum, and Plasma, *Biochem J* **30** 1119, 1936. (c) Farmer and Abt.<sup>2</sup>

5 King, C. G. Vitamin C, Ascorbic Acid, *Physiol Rev* **16** 238, 1936.

6 Abbasy, M. A., Harris, L. J., Ray, S. N., and Mairack, J. R. Diagnosis of Vitamin C Subnutrition by Urine Analysis, *Lancet* **2** 1399, 1935. Harris, Ray, and Ward.<sup>31</sup> Johnson and Zilva.<sup>32</sup>

7 Ralli, E. P., Friedman, G. J., and Kaslow, M. An Excretory Test for Vitamin C Deficiency and Subnutrition, *Proc Soc Exper Biol & Med* **36** 52, 1937. Finkle.<sup>33</sup>

a decreased intake<sup>8</sup> We were interested in finding whether there are anomalies of utilization and storage in other clinical conditions, as determined by the rate of saturation, excretion and rise in blood concentration

#### EXPERIMENTAL PROCEDURE

Each patient saved all the urine of each twenty-four hours in a stoppered amber bottle The specimen was kept in the refrigerator and preserved with twice-normal sulfuric acid, 10 per cent by volume, and then titrated with 2, 6-dichlorophenolindophenol This acid was chosen because of its greater efficiency in preventing oxidation<sup>9</sup>

The blood was drawn in the morning before any vitamin C was taken, hence it was a fasting specimen even though the patient might have taken some other foods Determinations of the vitamin in the blood were made at frequent intervals but not daily The method used was a modification of the one described by Farmer and Abt<sup>2</sup> About 7 cc of blood was oxalated and centrifuged, 2 cc of the supernatant serum was removed, and to it were added 4 cc of distilled water, 2 cc of 5 per cent sodium tungstate and 2 cc of third-normal sulfuric acid, this was again centrifuged, and 4 cc of the supernatant fluid was used for titration instead of 2 cc as recommended by Farmer and Abt This was titrated immediately with sodium 2,6-dichlorobenzenoneindophenol, but while the recommended dilution of this dye is about 1 5,000, we used a dilution of 1 20,000 This reduced the percentage of error, since a greater amount of solution was required to produce the end point In a portion of the experiment we further modified this technique by the addition of potassium cyanide (KCN) to the oxalated blood This, according to Pijoan and Klemperer,<sup>10</sup> prevents the oxidation of the ascorbic acid, and higher values are obtained We also found this to be the case The values obtained by the use of this modification are distinguished by the addition of "KCN"

The patients and controls were first on ward diets, then they were put on vitamin C-free diets, and 400 mg of ascorbic acid was administered daily in tablet form, divided into two doses The initial level of the ascorbic acid excreted was noted, along with the rate of the rise in excretion, the rapidity with which saturation was attained and the changes in the plasma concentration of ascorbic acid The excretion of 75 per cent or more of the 400 mg dose was considered by us as a sign of saturation

#### SCURVY

Chick and Hume<sup>11</sup> in 1917 and Cohen and Mandel<sup>12</sup> in 1918 furnished experimental proof of the correctness of the old theory that

8 Abbasy, M A , Harris, L J , and Hill, N G Vitamin C and Infection Excretion of Vitamin C in Osteomyelitis, *Lancet* **2** 177, 1937 Bullowa, J G M , Rothstein, I A , Ratish, H D , and Harde, E Cevitamic Acid Excretion in Pneumonia and Some Other Pathological Conditions, *Proc Soc Exper Biol & Med* **34** 1, 1936 Harris, L J , Passmore, R , and Pagel, W Influence of Infection on Vitamin C Content of Tissues of Animals, *Lancet* **2** 183, 1937

9 Youmans, Corlette, Akeroid and Frank<sup>13, 14</sup> Johnson Silva<sup>15</sup>

10 Pijoan, M , and Klemperer, F Determination of Blood Ascorbic Acid, *J Clin Investigation* **16** 443, 1937

11 Chick, H , and Hume, E W The Distribution Among Foodstuffs (Especially Those Suitable for Rationing of Armies) of the Substances Required for the Prevention of Beriberi and Scurvy, *J Roy Army M Corps* **29** 121, 1917



scurvy is due to deficiency of a substance found in fresh fruits and vegetables. This substance is now known to be ascorbic acid. Until recently the diagnosis of scurvy was based on three factors: (1) a history which demonstrated deficiency of vitamin C-containing foods in the diet, (2) symptoms and findings in reference to the gums, hemorrhages, fragility of the superficial and deep capillaries, and subperiosteal hemorrhages in children and (3) therapeutic results. Any or all of these may be erroneous or unreliable for a positive diagnosis. An accurate or reliable history in reference to consumption of vitamin C-containing foods may be difficult to obtain. Often it is difficult to get an accurate account of a patient's diet for a long period. Short periods of consumption of foods rich in vitamin C may be overlooked, and yet during such periods sufficient storage of ascorbic acid may have occurred to make subsequent deficiency harmless. Likewise vitamin C-containing foods may be consumed but not utilized by reason of diarrhea, vomiting or destruction by intestinal bacteria.<sup>12</sup> Also, certain foods vary greatly in their content of this vitamin, depending on the manner of their use, storage and distribution. Among these may be mentioned milk, which has considerable vitamin C originally but loses it rapidly on pasteurization and exposure to light and air, dried fruits, which contain a negligible amount of vitamin C, and fresh fruits, the processing of which entails a considerable loss of vitamin C.<sup>13</sup>

The symptomatic picture may be incomplete and insufficient for certain diagnosis. The gum symptoms are absent in edentulous persons and in persons with mild deficiency. The subcutaneous and other hemorrhages may be due to purpura of other causation, and the capillary fragility test may be negative in a patient with true scurvy or positive in a nonscorbutic person.<sup>14</sup>

The therapeutic test of giving a vitamin C-rich diet may be objected to in that other substances are supplied in this diet which may be responsible for the improvement rather than vitamin C. Coincidental spontaneous remission of a condition other than scurvy must be considered

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12 Cohen, B., and Mandel, L. B. Experimental Scurvy of the Guinea Pig in Relation to Diet, *J Biol Chem* **35** 425, 1918

13 Marin, P. Scorbuto da distruzione batterica intestinale di vitamina C? *Minerva med* **2** 25, 1936

14 Kahn, S. K. Influence of Certain Agents on the Lability of the "Reducing Factor" (Vitamin C) in Milk, *Nature, London* **132** 446, 1933, Lability of the "Reducing Factor" (Vitamin C) in Milk, *ibid* **132** 64, 1933. King.<sup>5</sup>

15 Armentano, L. Hamorrhagische Diathese und Vitamin C. Der Nachweis der Hypovitaminosen aus dem Harn, *Ztschr f klin Med* **129** 685, 1936. Baumann, T., and Rappolt, L. Untersuchungen zum C-Vitaminstoffwechsel. Untersuchungen über die Beziehungen der Festigkeit der Hautkapillaren (Kapillarresistenz) zu dem Sättigungsgrad des Organismus an C-Vitamin, *Ztschr f Vitaminforsch* **6** 43, 1937

Recent studies on vitamin C excretion and saturation throw some additional light on the subject. However, all these reports dwell on the quantitative difference between scorbutic and nonscorbutic persons in relation to vitamin C, and most of the studies of scurvy in adults deal only with the urinary excretion of the vitamin.

A case of scurvy in an adult was reported by Wood<sup>16</sup> in which there was no excretion of vitamin C in the urine, and even after the patient received 1,000 mg of ascorbic acid by mouth only 17 mg was excreted. In Schultzer's<sup>17</sup> 3 cases and in the case reported by Archer and Graham<sup>18</sup> the initial amounts excreted were only slightly below the amounts excreted by the controls. The observers administered the vitamin both by mouth and by vein in varying amounts and both in the form of orange juice and in that of pure ascorbic acid. Their patients showed difficulty in saturation, i. e., it required prolonged high vitamin feeding to produce saturation. Archer and Graham noted that their patient excreted only 51 per cent of the intake after three weeks, while their controls excreted 75 per cent of the intake after several days to one week. Nisenson and Cohen<sup>19</sup> recently reported a case of scurvy in an adult whose initial excretion was 175 mg in twenty-four hours. A test dose of 600 mg produced no rise. Then 280 mg and 330 mg were given daily for eight days each. The excretion remained around 65 mg until the twelfth day, when a perceptible rise occurred and higher levels were maintained. On the tenth day of this treatment the patient appeared entirely well. However, the tourniquet test was still slightly positive on the eighteenth day.

The studies of the ascorbic acid in the blood were done chiefly on infants with scurvy. One of the first reports was by Abt and Epstein,<sup>20</sup> who gave exceptionally high values for scorbutic infants. One patient had an initial value of 0.97 mg per hundred cubic centimeters of blood and another 1.02 mg, both of these values are now considered normal values. Ingalls<sup>21</sup> reported a study of 15 children with scurvy with examinations of the blood and urine. The concentration in the blood of this group of patients was extremely low and varied from 0.0 to 0.16 mg per hundred cubic centimeters. The ascorbic acid excreted

16 Wood, P. A Case of Adult Scurvy. *Lancet* **2** 1405, 1935.

17 Schultzer, P. On Saturation of Scorbutic Patients with Ascorbic Acid, *Acta med. Scandinav.* **88** 317, 1936.

18 Archer, H. E., and Graham, G. Some Observations on Excretion of Ascorbic Acid, *Lancet* **1** 710, 1936.

19 Nisenson, A., and Cohen, A. Adult Scurvy. Study of Urinary Output of Cevitamic Acid, *Am. J. M. Sc.* **194** 63, 1937.

20 Abt, A. F., and Epstein, I. M. Cevitamic Acid (Ascorbic Acid) in the Treatment of Infantile Scurvy, *J. A. M. A.* **104** 634 (Feb. 23) 1935.

21 Ingalls, T. H. Studies on the Urinary Excretion and Blood Concentration of Ascorbic Acid in Infantile Scurvy, *J. Pediat.* **10** 577, 1937.

in the urine was nil. This group of patients was not carried to saturation. Ingalls and Warren<sup>22</sup> also studied patients who were kept for a long time on a diet for the cure of peptic ulcer, whose condition they classified as asymptomatic scurvy, and reported that the values for ascorbic acid in the blood were in the same range as those in frank scurvy, namely, an average of 0.19 mg per hundred cubic centimeters. These patients when given massive doses of vitamin C showed a rapid rise in the blood ascorbic acid. Taylor and co-workers<sup>10</sup> reported determinations of blood ascorbic acid in clinical cases of scurvy as ranging from 0.11 to 0.55 mg per hundred cubic centimeters. They also studied the response of their patients to 1 Gm. of ascorbic acid administered intravenously. A patient whose case they reported showed a rise in the blood ascorbic acid to 2.58 mg per hundred cubic centimeters in thirty minutes, the concentration then fell in one and a half hours to 1.24 mg. This value was maintained for forty-eight hours. However, the initial value for the blood ascorbic acid of this patient was 0.61 mg, which indicates that he had been receiving antiscorbutic therapy prior to this experiment, nor is it stated whether he had been on a scorbutic diet during these twenty-four hours.

From these reports we gather that patients suffering from clinical scurvy have low concentrations of ascorbic acid in their blood and urine, but corresponding determinations may be just as low or indeed lower for some persons who show no signs of clinical scurvy. This seems paradoxical and makes one wonder whether the small amount of ascorbic acid in the body is in itself the factor responsible for the symptoms of scurvy. Indeed there is a suggestion that in clinical scurvy there may be some anomaly in storage, as evidenced by the lower percentage excreted after prolonged feeding reported by Archer and Graham.<sup>18</sup>

CASE 1—J. W. S., a man aged 28, was admitted to the medical ward of the hospital Jan. 7, 1937, complaining of pain in both thighs of one month's duration, black and blue areas on the right leg and thigh of ten days' duration and small red spots on both legs for two weeks. Limping because of the pain in the left leg was present for one week and weakness for several days. In the past five or six years there had been profuse bleeding from small cuts, and bleeding from the gums had been troublesome since 1928. In 1934 he noted pinpoint and pinhead sized purple spots over his legs and a loss of 12 pounds (5.4 Kg.) in weight. The dietary history revealed a complete abstention from citrus fruits and fresh vegetables. The patient stated that he had eaten no oranges or lemons for two years and no tomatoes, grapefruit or fresh vegetables in the last six years. His diet consisted almost exclusively of meat sandwiches, pie, doughnuts and coffee.

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<sup>22</sup> Ingalls, T. H., and Warren, H. A. Asymptomatic Scurvy. Its Relation to Wound Healing and Its Incidence in Patients with Peptic Ulcer, *New England J. Med.* **217** 443, 1937.

The essential physical findings were as follows. All the teeth that were present were in an advanced state of caries, with many of the teeth buried below the gum surface and some projecting above the gum margin only a very short distance. The gums were not spongy and bled only slightly, but there were some areas of hyperemia. The mucous membranes of the pharynx and mouth were pale. The lower extremities revealed petechial hemorrhages, follicular in distribution, ecchymoses of the left thigh and lower part of the left leg and also of the right foot, and brawny induration of the muscles of the calves and right thigh. The left knee was swollen and tender, and the patient was unable to extend it completely. The left foot was held in equinovarus. The tourniquet test with a pressure of 80 mm of mercury for three minutes was strongly positive.

The laboratory findings were moderate secondary anemia, a normal platelet count, a normal coagulation time and a normal bleeding time.

Roentgen examination of the chest, left hip joint and tibiae showed no abnormality. The teeth showed absorption around the roots.

CASE 2—A. P., a man aged 69, entered the medical ward of the hospital June 10, 1937, complaining of bluish discoloration and pain in the calves present for six months and bleeding of gums and loosening of teeth, present for three years. Because of his poor financial circumstances his diet had consisted for the last twelve years of bread, pork, beans and coffee. In the last few years he had not eaten any fresh vegetables, oranges, lemons or limes or other fruits. He had been in fair health until three years before examination, when he began feeling weak and lost some weight. At that time his teeth began to loosen and his gums became swollen and began bleeding. Several teeth fell out. Six months before entering the hospital he noticed that the skin over the calves became blue and discolored and that the muscles became hard and very tender.

The physical findings included large ecchymoses of both the upper and the lower extremities and petechial hemorrhages of the legs. Characteristic induration and tenderness of the hamstring and quadriceps femoris muscles were also detected.

Patient J. W. S. (table 1) was on a ward diet with abundant vitamin C feedings for four days before the experiments were begun, and the basal excretion of ascorbic acid varied between 14.95 and 23.49 mg, with only two twenty-four hour periods in which it was 20 mg or above. Patient A. P. (table 1) showed a much lower basal excretion, between 9.51 and 13 mg. Thus it may be seen that from the basal excretion alone the values for the first patient would fall almost within or just slightly below the normal limits. The second patient, while having low initial excretion, would still be thought to have values compatible with mild subclinical vitamin C deficiency. Hence our determinations of basal excretions of ascorbic acid were not diagnostic, as was pointed out also by Schultzer<sup>17</sup> and by Archer and Graham<sup>18</sup>. Why this should be so is difficult to explain except by the assumption that there are small amounts of other substances in the urine, such as thiosulfates and ergothioneine,<sup>6</sup> up to 6 mg, which may reduce the dye. In the lower ranges this interference may considerably distort the results, whereas in the higher ones the influence on the results would be inconspicuous. The

fact that the patients were on a vitamin-rich diet just before the experiment was begun may be of some importance

After the administration of large doses of ascorbic acid was started, a striking difference was noted. Patient J W S showed no sharp rise in excretion of the vitamin until 2,800 mg had been given, and the highest excretion ever obtained was 271.2 mg, or 68 per cent of the

TABLE 1—*Ascorbic Acid in Blood and in Urine of Patients with Scurvy*

Day	Diet	A P—Male		J W S—Male	
		Mg Ascorbic Acid		Mg Ascorbic Acid	
		24 Hr Collection of Urine	100 Cc Blood Plasma	Diet	In 24 Hr Collection of Urine
1	Ward	9.51	0.3	Ward*	16.0
2		12.45			15.77
3		15.0			18.74
4	Vitamin C-free diet plus 400 mg C†	Lost			20.0
5		20.25			18.77
6		13.82	0.36		17.45
7		Lost			23.40
8		10.67			19.66
9		41.22		Vitamin C-free diet plus 400 mg C	27.2
10		10.72			20.88
11		120.45			28.6
12		45.29			31.5
13		21.68			24.7
14		26.45			29.1
15		151.05			37.7
16		175.5			150.9
17		212.09			205.8
18		268.08	0.79		214.83
19		193.93			191.6
20		215.04			215.7
21		187.05			229.2
22		258.75			252.12
23		223.14			226.8
24		245.76	0.92		250.2
25		273.0			261.0
26		265.2			271.2
27		221.56	0.63		
28		130.0			
29		220.83			
30		181.81	0.76		
31		173.2			
32		165.75			
33		242.4	0.94		
34		212.06			
35		291.09			

\* Patient J W S was on a ward diet with abundant vitamin C feedings before the experiments began. With day 1 of the experiment recorded here he was placed on the ward diet alone—a low vitamin diet.

† Doses of 400 mg were given from day 4 to days 12, 13 and 14 when doses of 200.0 and 200 mg, respectively, were given. On all subsequent days the doses were again 400 mg.

intake, although eighteen daily doses of 400 mg were administered. In other words, saturation was not obtained although 7.2 Gm of ascorbic acid was administered. The case of patient A P was even more striking in this respect. Although a sharp rise occurred on the eighth day of the administration of large doses of the vitamin and after 4,000 mg had been given 268 mg was excreted, the amount excreted then dropped from this value and a saturation value was not reached until a total of 12 Gm had been taken. The excretion values oscillated sharply

and were below 200 mg thirty days after the daily administration of 400 mg was begun

It will be seen that all the controls reached this point quickly, i. e., in seven days or less (table 2), and showed a rise in excretion of ascorbic acid on the first day. The exhausted subjects showed a rise in excretion of ascorbic acid on the third to sixth day and saturation several days later.

The studies of the blood plasma revealed even more interesting results. The control patients (table 2), although they were slightly undernourished with respect to vitamin C, showed a basal level of 0.52 mg and 0.61 mg per hundred cubic centimeters of plasma. The latter value may be considered on the lower border of normal<sup>4a</sup>. The blood plasma showed a sharp rise from these relatively low values soon after the high ascorbic acid dosage was started. One control (J. K.) showed 1.44 mg of ascorbic acid per hundred cubic centimeters of blood plasma on the fifth day of high vitamin dosage, when the amount excreted in the urine was 144 mg. Another control (E. G.) showed 1.13 mg of ascorbic acid per hundred cubic centimeters of blood plasma one day after the administration of the acid was started and when the amount excreted in the urine was only 78.85 mg. In other words, these controls and other nonscorbutic persons showed a rapid rise of ascorbic acid in the blood plasma to 1.1 mg per hundred cubic centimeters or higher after one or several large doses of the acid (chart 1, table 2) and even before the urinary excretion reached a high level. The ascorbic acid in the blood, unlike that in the urine, reaches a certain level above which it does not go regardless of the amount of vitamin C given. Thus, in subject E. G. the plasma level was 1.13 mg at 78.85 mg urinary output, and at 370 mg urinary output it was the same. In control J. K. the plasma value was 1.44 mg at 144 mg urinary excretion and only 1.21 mg at 303 mg excretion. With this method without the use of potassium cyanide (KCN) the value for ascorbic acid in the blood plasma during fasting was never above 1.54 mg per hundred cubic centimeters.

Now contrast the behavior of the plasma ascorbic acid of the scorbutic patient (A. P.) with that of the plasma ascorbic acid of the controls. After twelve daily 400 mg doses the blood plasma value was 0.59 mg per hundred cubic centimeters, and this when the urinary value was 268 mg. The scorbutic patient can apparently excrete large quantities in the urine while the concentration in the plasma remains low. While the plasma value rose to 0.92 mg per hundred cubic centimeters on the eighteenth day, it fell to 0.63 mg after twenty-two consecutive days of high vitamin feeding. Such behavior, which may indicate a low renal threshold, has not been observed by us in any other condition and may

TABLE 2—Summary of Urinary Excretion and Blood Concentration of Ascorbic Acid for Various Subjects\*

Subject	Sex†	Average Basal Excretion per 24 Hr	First Excretion Peak		Highest Excretion Peak	Days of High Vitamin Feeding	Average Daily Excretion from Peak to End of Experiment	Ascorbic Acid per 100 cc Blood Plasma		Comment
			Dayst	Height				Lowest	Highest	
Normal										
E G	M	16.4	1	78.85	356.3	7	232	0.61	1.13	Compensated hypertensive heart disease
J H	F	25.05	1	156.2	336.0	3	279			Neurosis
J G	F	25.22	1	108.13	334.66	8	2.3			Compensated rheumatic heart disease
J K	M	14.9	4	94.69	336.96	16	242	0.52	1.14	Slightly exhausted, compensated rheumatic heart disease
Exhausted										
C J	M	14.2	6	140.8	310.5	11	266	0.38	1.47	Peptic ulcer
W Von B	M	17.4	3	99.5	369.0	11	245	0.32	1.19	Peptic ulcer
Hyperthyroid										
J K	F	19.65	1	85.86	276.76	12	183	1.40 (KCN)	1.92	
B D	F	12.7	5	72.67	269.22	14	196			
F W	M	19.65	3	81.90	228.12	10	188			
E H	F	11.19	5	110.0	230.33	13	184	0.69 (KCN)	1.37	
L L	F	14.19	3	111.28	296.0	17	226	0.77 (KCN)	1.90	
J B	F	19.94	2	96.0	263.0	14	188	0.78 (KCN)	1.74	
J G	F	57.03	1	91.8	256.5	10	187			
Patients with Malignant Tumors										
A C	M	7.1	3	41.0	218.8	24	142			Carcinoma of lung with metastasis to spine
M L	M	7.88	5	70.07	259.4	17	182	0.66 (KCN)	1.70	Carcinoma of stomach
M C	F	10.04	3	40.32	207.72	9	135			Carcinoma of stomach
J W	M	11.53		None	18.76	11				Carcinoma of lung patient died of melanosisarcoma
A M	F	13.68	4	112.2	220.5	10	193			
Patients with Slow Growing Malignant Tumors										
A K	F	13.9	1	81.89	331.3	15	239	1.04 (KCN)	1.43	Metastatic carcinoma to spine 10 yr after primary lesion of breast
Patients Suspected to Have Malignant Tumors										
G K	M	12.1	3	81.0	330.0	10	238	0.69 (KCN)	1.9	Proved later to be chronic ulcer
B S	F	3.82	4	192.2	338.0	10	267	0.53 (KCN)	2.31	Symptoms and findings disappeared
E F	M	6.77	5	57.94	328.95	17	230	0.57 (KCN)	1.64	Symptoms and findings disappeared

\* All values given in milligrams

† F indicates female M male

‡ Days of high vitamin dosage

be an anomaly peculiar to the scorbutic organism, i. e., a person suffering from clinical scurvy not only may have a deficiency of the substance in the body but may also be unable to store it satisfactorily

# PURPURAS

Although it should be unnecessary to point out that not all hemorrhagic diseases are dependent on vitamin C deficiency, still there has been in the literature a good deal of reference to the favorable effect of ascorbic acid on nonscorbutic hemorrhagic conditions<sup>23</sup> with the implication that there may be a deficiency of ascorbic acid in some of these<sup>24</sup>. Those who published these reports did not claim, however, that there

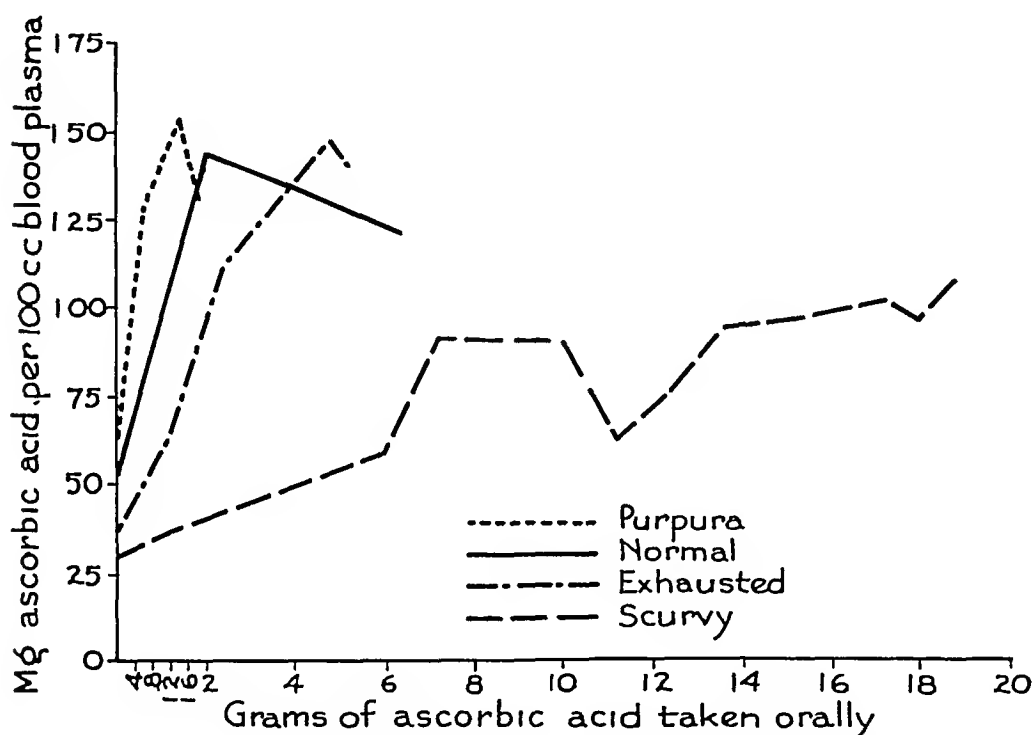


Chart 1—Concentration of ascorbic acid in the blood plasma of scorbutic and nonscorbutic persons

is a cause and effect relationship between the various purpuras and vitamin C. At times considerable diagnostic difficulty is encountered in ruling out scurvy in certain nonthrombopenic purpuras.

In fact, such was the case with our patient J. B. (table 3), who had a history suggestive of vitamin C malnutrition, some bleeding from the gums, a positive tourniquet test and profuse spontaneous subcutaneous and mucous membrane hemorrhages. Patient E. N. also gave a history of restriction of fresh fruits and vegetables due to various gastro-

<sup>23</sup> Cotti, L., and Larizza, P. Ueber den Einfluss der Ascorbinsäure auf die Blutgerinnung. Untersuchungen über den Wirkungsmechanismus "in vivo" der Ascorbinsäure in normalen und pathologischen Verhältnissen, *Klin Wchnschr* **15** 227, 1936. Glanzmann, E. Zur Problem der Purpura fulminans, *Schweiz med Wchnschr* **67** 829, 1937.



intestinal disturbances. She also had bleeding from the gums, subcutaneous ecchymosis and a mildly positive tourniquet test. Both of these patients had normal platelet counts and normal bleeding and coagulation times. A diagnosis of scurvy was strongly entertained until the studies of ascorbic acid were completed (table 3). These studies showed completely normal behavior. The immediate rise of ascorbic acid in the blood even while the amount excreted in the urine was low is especially striking when compared with the behavior of this vitamin in the scorbutic patient.

E. M. is a patient with true thrombopenic purpura who was studied for purposes of comparison. His response was completely normal.

TABLE 3—Patients with Purpura

Days	J B—Female				L M—Male				I N—Female			
	Diet	Mg Ascorbic Acid			Diet	Mg Ascorbic Acid			Diet	Mg Ascorbic Acid		
		24 Hr Collec tion of Urine	100 Cc KCN	Blood Plasma No KCN		24 Hr Collec tion of Urine	100 Cc Blood Plasma	24 Hr Collec tion of Urine		100 Cc Blood Plasma		
1	Ward		0.95	0.66	Ward	15.6			Ward		0.96 KCN	
2		27.1				8.47				21.78		
3		23.9	0.99	0.63		10.16				17.71		
4		22.82				12.74				15.63		
5	Vitamin C-	31.24	1.6	1.28		15.9	1.19		Vitamin C-	16.10		
6	free diet	162.44				5.26	KCN		free diet	55.75	1.99	
7	+ 400 mg	255.34	1.78	1.54		7.95	1.13		+ 400 mg	227.50		
8		336.0	1.75	1.50	Vitamin C-	118.4				378.75		
9		336.0			free diet	117.9				260.3	2.69	
10					+ 400 mg	283.12				308.25		
11						178.2	1.76			328.25		
12					"	140.49						
13					"	97.2	1.51					
14					"	312.84						
15					"	333.3						
16					"	333.3	1.7					

While 1 of these patients, J. B., showed a favorable response to the high doses of ascorbic acid, this response appeared to be merely coincidental, since the symptoms recurred later in spite of continuance of this medication.

HYPERTHYROIDISM

According to the work of Szent-Gyorgyi,<sup>24</sup> Tauber and co-workers<sup>25</sup> and others, the most likely action of ascorbic acid is in the capacity of an enzyme for cellular oxidation. By virtue of its strong reducing power it aids in the process of oxygen exchange. It has also been shown<sup>24</sup> that scorbutic tissues take up less oxygen in vitro than normal tissues. These theoretic considerations led us to investigate the role of ascorbic acid in hyperthyroidism. During this investigation we

24 Szent-Gyorgyi, A. Function of Hexuronic Acid in the Respiration of the Cabbage Leaf, *J. Biol. Chem.* **90** 385, 1931.

25 Tauber, H., Kleiner, J. S., and Mishkind, D. Ascorbic Acid Oxidase, *J. Biol. Chem.* **110** 211, 1935.

became aware of the work of Mosonyi,<sup>26</sup> who found that guinea pigs rendered hyperthyroid by medication with thyroid and thyroxin showed less tissue storage of the vitamin than similarly fed normal animals. He concluded that this phenomenon may be due either to increased excretion or to increased utilization. He did not make any studies of excretion on these animals.

All our hyperthyroid patients excreted less than 300 mg of ascorbic acid on the daily 400 mg doses, i. e., their excretion was always below what we should have expected in a normal person. The blood plasma showed normal saturation. Although most of these patients were on a high caloric diet that included an abundance of fresh fruits and vegetables, only 2 patients, J. K. and J. G., showed normal storage, as judged by the response to the first large dose. One of these patients (J. K.), although having a high initial concentration of ascorbic acid in the blood, excreted less than an average of 20 mg per day, which also is evidence of increased utilization.

Further evidence of increased utilization is the average of the daily twenty-four hour amounts excreted from the first peak to the end of the experiment (table 2). This was below 200 mg in all patients with hyperthyroidism except L. L., while the normal persons and the exhausted patients all showed an average of around 250 mg. The longer such an experiment was continued, the greater this difference would become, since the normal persons would continue having values of 300 mg or above and the hyperthyroid patients would continue to show the lower levels of excretion.

One of our patients with hyperthyroidism, J. B., was studied both before and after thyroidectomy. Chart 2 shows a comparison of the amounts of ascorbic acid excreted in the urine during these two periods. The difference is marked. In the post-thyroidectomy period, when her basal metabolic rate was around  $\pm 0$  per cent, most of the values for daily excretion of ascorbic acid were above 250 mg, and the highest was 330 mg, while before thyroidectomy all except a single day's excretion were below 250 mg. The average of the daily values after the initial rise was 198 mg before thyroidectomy and 250 mg after thyroidectomy, or an increase of over 20 per cent.

#### MALIGNANT TUMORS

Several different investigators showed some relation between experimental malignant tumors and vitamin C. Musulin and co-workers<sup>27</sup>

26 Mosonyi, J. Einfluss des Schilddrussenhormons auf den Vitamin C-Stoffwechsel, *Ztschr f physiol Chem* **237** 173, 1935.

27 Musulin, R. R., Silverblatt, E., King, C. G., and Wood, G. E. Titration and Biological Assay of Vitamin C in Tumor Tissue, *Am J Cancer* **27** 707 1936.

found that Philadelphia no 1 sarcoma had increased reducing power, and this was proved to be due to vitamin C by animal feeding experiments. Watson<sup>28</sup> showed the same to be true of the Jensen and the Walker sarcoma and of spontaneous mammary carcinoma. Benign tumors were shown to have much lower reducing power.<sup>27</sup> Voegtlin and associates,<sup>29</sup> using several different methods of determination, came to essentially the same conclusion. Vogelaar and Erlichman<sup>30</sup> showed

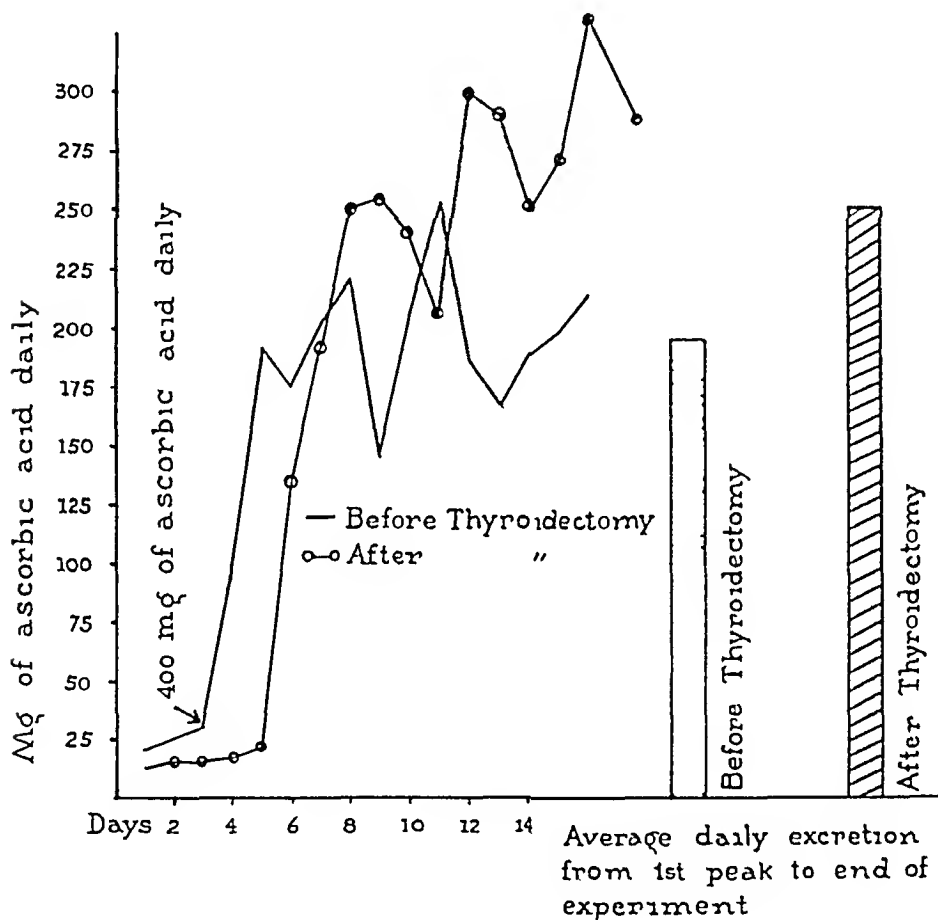


Chart 2—Excretion of ascorbic acid in the urine of a patient with hyperthyroidism, (J B, a woman aged 31) before and after thyroidectomy

28 (a) Watson, A F The Chemical Reducing Capacity and Vitamin C Content of Transplantable Tumors of Guinea Pigs and Rats, *Brit J Exper Path* **17** 124, 1936 (b) Watson, A F, and Mitole, M A Note on the Reducing Activity of the Tissues of Normal and Tumor Bearing Rats and Mice, *Biochem J* **28** 811, 1934

29 Voegtlin, C, Kahler, H, and Johnson, J M The Colorimetric and Spectrophotometric Determination of Vitamin C in Malignant Tumors, *Am J Cancer* **29** 477, 1937

30 Vogelaar, J P M, and Erlichman, E Significance of Ascorbic Acid for the Growth in Vitro of Crocker Mouse Sarcoma 180, *Am J Cancer* **31** 283, 1937

that ascorbic acid added to the artificial culture mediums in which the Crocker mouse sarcoma was grown stimulated cell division, inhibited cell degeneration and seemed to be necessary for the formation of intercellular fibers. Gordonoff and Ludwig,<sup>31</sup> however, found that "scorbutic mediums" produced almost as good cultures of malignant cells and fibroblasts as mediums containing vitamin C. Havas<sup>32</sup> showed that tumors of tomato plants treated with ascorbic acid attained twice as great a size as the nontreated tumors.

It seems logical to assume from physiologic considerations that rapidly growing malignant tumors use greater amounts of ascorbic acid by virtue of their rapid growth and hence more rapid oxidative processes. This was partly confirmed by the observation<sup>28a</sup> that tumor-bearing animals become more rapidly scorbutic than nontumor-bearing controls. We were interested in determining whether human beings suffering from various forms of malignant tumors would yield any confirmatory evidence for these theoretic considerations. Our subjects with malignant tumors included patients with gastric carcinoma, melanoma and carcinoma of the lung with metastasis. All of these patients were selected as being completely afebrile, to avoid a confusing issue, none of them vomited or showed any evidence of increased utilization as judged by the amount excreted in the urine. None of these patients excreted over 300 mg in twenty-four hours, and the average amount excreted daily from the first peak to the end of the experiment was between 135 and 193 mg (table 2). J. W., a patient very ill with carcinoma of the lung, showed no increase in excretion of ascorbic acid after eleven daily 400 mg doses. We felt that this was significant even though the patient was so ill that some loss of urine might have occurred.

We present also a group of 3 patients who were studied because the clinical and roentgen findings pointed strongly toward a diagnosis of malignant tumor. However, the studies of the urinary excretion showed a normal response (table 2). All of these patients are still alive, and the subsequent course of illness in each proves that the condition is nonmalignant. Patient G. K. continues having stationary roentgen findings, has gained weight since he was first studied in August 1937 and maintains his hemoglobin level and general health. The other 2 patients showed complete disappearance of the roentgenographic findings with clearing up of the clinical picture.

This observation may be of value as an aid in distinguishing a benign from a malignant lesion. The length of time of the urinary studies may be abbreviated in practice by giving the patient the 400 mg doses of

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31 Gordonoff, T., and Ludwig, F. Ueber die Bedeutung der Vitamin für die Krebstherapie, *Ztschr. f. Krebsforsch.* **46** 73, 1937.

32 Havas, L. Ascorbic Acid and Phytocarcinomata, *Nature*, London **136** 989, 1935.

ascorbic acid in addition to the usual diet for ten days or two weeks, until saturation has practically occurred. The patient can then be put on the scorbutic diet plus the pure ascorbic acid and the urine collected for one week or ten days, if in this length of time a normal excretion does not occur, the observation may be accepted as a sign of increased utilization, and hence a sign pointing to malignant growth.

A single patient with a malignant tumor (A K) among those whom we studied showed a response within normal limits to the high vitamin dosage. This patient had a mastectomy for carcinoma ten years previously. She had a recurrence of cutaneous lesions four years ago, which responded to roentgen treatment, and now, ten years after the removal of the primary tumor, she has what appears roentgenographically to be metastatic lesions of the thoracic spine, her general condition remaining good. This finding in no way refutes our original tenets, since this malignant tumor would appear from its duration to be very slow growing and relatively benign. A tumor of this type would be expected to have oxidative processes almost as slow as those of normal tissues and hence would be expected to use little ascorbic acid.

#### LEUKEMIA

Because of the rapid cellular proliferation in the hyperplastic bone marrow and the great acceleration in the production of leukocytes in this disease we thought there might be some increased utilization of ascorbic acid. We are not aware of any studies made of the concentration of ascorbic acid in the blood and urine in leukemia. A favorable therapeutic effect, however, was reported by Eufinger and Gaetgens,<sup>33</sup> who claimed to have influenced the blood picture and clinical picture of their patient favorably by intravenous administration of crystalline ascorbic acid.

Our patient was afebrile, and his general condition was good. He was studied before and after total thyroidectomy to determine what influence the thyroid had on the utilization of ascorbic acid in leukemia. Chart 3 shows a comparison in this respect between a normal person and our patient with leukemia. Although their basal excretions of ascorbic acid were along the same level, in the leukemia patient before thyroidectomy no rise in excretion occurred until the eleventh day, and the amount excreted was never above 228 mg per day, although the high vitamin feeding was continued for nearly thirty days. At the beginning of the experiment this patient's basal metabolic rate was +11 per cent, later determinations were +24 and +35 per cent. Thyroidectomy was performed, and the basal metabolic rate decreased to only -2 per cent, although the patient had some signs of myxedema.

<sup>33</sup> Eufinger, H., and Gaetgens, G. Ueber die Einwirkung des Vitamin C auf das pathologisch veränderte weisse Blutbild, *Klin Wchnschr* 15 150, 1936.

The second curve showed an earlier rise in excretion, and on the twentieth day of the high vitamin feedings the amount was above 300 mg. However, there was a period of very low, almost basal excretion from the thirteenth to the eighteenth day. With these exceptions the curves are almost the same. It seems apparent that the thyroid had only slight influence on the increased utilization of ascorbic acid in this case, since the average daily amount excreted from the first peak to the end of the experiment was the same (chart 3).

The blood plasma concentration never reached so high a level as was observed in the normal persons or in the other patients with

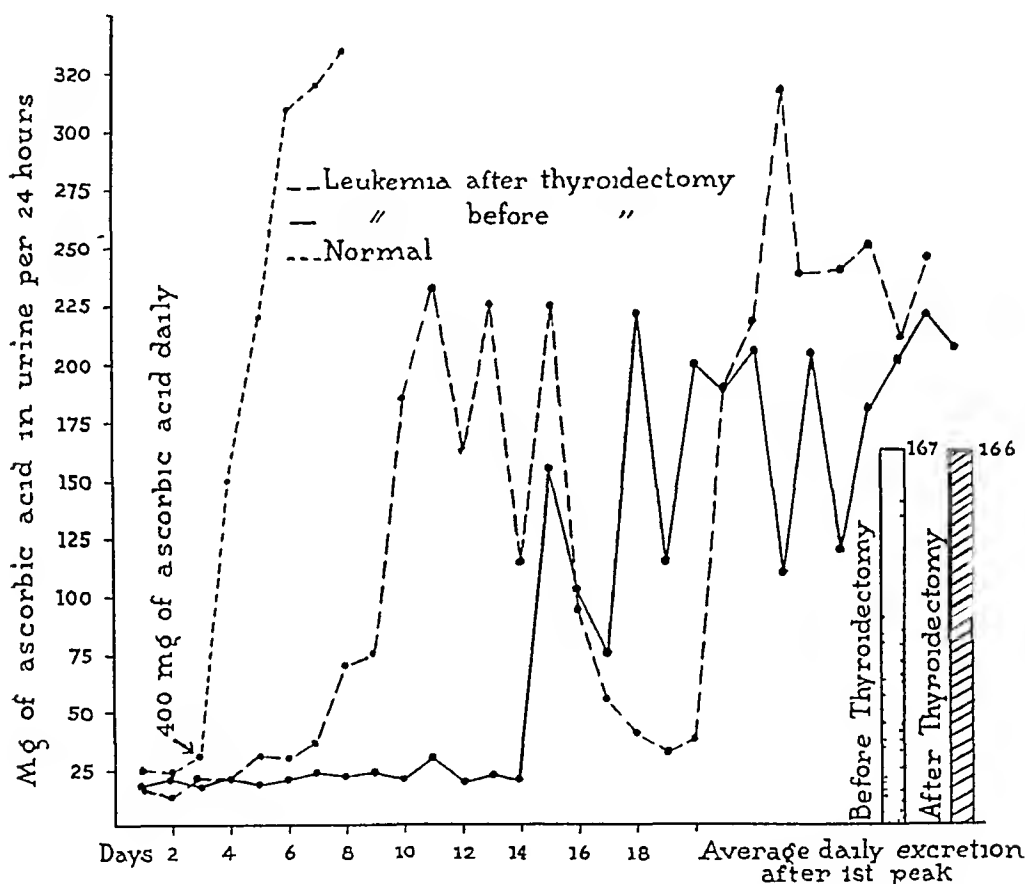


Chart 3—Excretion of ascorbic acid in the urine of a normal person and in that of a patient with leukemia before and after thyroidectomy

increased utilization. As regards the patients with hyperthyroidism and malignant tumors, although their urinary excretion of ascorbic acid was on the order of that of the leukemic patient, their blood concentration at saturation levels was 1.5 mg per hundred cubic centimeters or above, whereas the leukemic patient did not show concentrations above 1.2 mg before thyroidectomy, and after thyroidectomy the highest level was 1.29 mg. There was a further decrease from this value to 1.14 mg at the time when the excretion of ascorbic acid was highest. These slightly lower values are probably of no significance.

## PEPTIC ULCER

Numerous reports have appeared dealing with the state of vitamin C nutrition in patients on diets for the cure of peptic ulcer. Drigalski<sup>34</sup> showed that with adherence to a strict ulcer diet for three weeks a decrease occurred in the ascorbic acid excreted. Archer and Graham<sup>34</sup> studied 9 patients with peptic ulcer who were on modified Sippy diets and found that their initial excretion of ascorbic acid varied from 8.5 to 26 mg. All of the values were lower than those for their 2 controls. They also showed a delayed rise in excretion of this substance on high vitamin feedings. They felt that this subclinical vitamin C deficiency was responsible for the poor healing found in some ulcerous patients after gastric surgical treatment. Ingalls and Warren<sup>35</sup> studied the blood ascorbic acid levels of 20 patients with peptic ulcer. All but 2 had very low levels, ranging from 0 to 0.6 mg. per hundred cubic centimeters. They called attention to the possible relation of vitamin C deficiency in these patients to wound healing and to hemorrhages. Rivers and Carlson<sup>35</sup> found correlations between capillary fragility and the concentrations of ascorbic acid in the blood and urine in their cases of bleeding peptic ulcer. In all but a single case there was decreased capillary fragility as demonstrated by the tourniquet test, and in all the cases the values for ascorbic acid in the blood and urine were subnormal. They feel that there is a possible causal relation between the increase in capillary fragility and the bleeding in this disease. They showed that the capillary resistance returned to normal after high vitamin C feedings.

Our patients on peptic ulcer diets showed evidence of vitamin C subnutrition as evidenced by urinary excretion of ascorbic acid in amounts below 20 mg. per twenty-four hours (table 2, chart 4), blood plasma concentrations of 0.3 to 0.4 mg. per hundred cubic centimeters, absence of response to 400 mg. doses of this vitamin till the third to sixth day and saturation after a week or ten days' feeding.

We were, however, primarily interested in the effect of alkaline medication on the absorption of ascorbic acid. Since this vitamin is highly unstable in alkaline solution in vitro, we thought that persistent medication with alkalis may interfere with absorption of the vitamin. On the basal milk and cream diet and 4 Gm. of alkalis every hour, patient W. P. (chart 4) excreted an average of 6.5 mg. of ascorbic acid per twenty-four hours for six days, after withdrawal of the alkalis he excreted 10.5 mg. per day for eight days. There was a prompt and persistent increase in excretion of the vitamin after the alkalis were

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34 Archer, H. E., and Graham, G. The Subcurvy State in Relation to Gastric and Duodenal Ulcer, *Lancet* 2:364, 1936.

35 Rivers, A. B., and Carlson, L. A. Vitamin C as Supplement in the Therapy of Peptic Ulcer. Preliminary Report, *Proc. Staff Meet., Mayo Clin.* 12:383, 1937.

stopped, although the diet was practically vitamin C free. When we began giving the large doses of ascorbic acid (chart 4), the patient received no alkalis until he was "saturated" (excretion, 300 mg). The addition of the alkaline powder caused a prompt drop in excretion of the vitamin, which persisted for six days and then rose to the previous level. If the alkaline medication or the neutralization of the hydrochloric acid in the stomach interfered with absorption of the vitamin, we should expect a continuance of the decreased excretion after the initial drop. Instead the excretion rose again in all cases to the previous high level. We interpreted this as meaning that the alkalis appeared to increase the amount of vitamin stored in the tissues—a sort of "super-

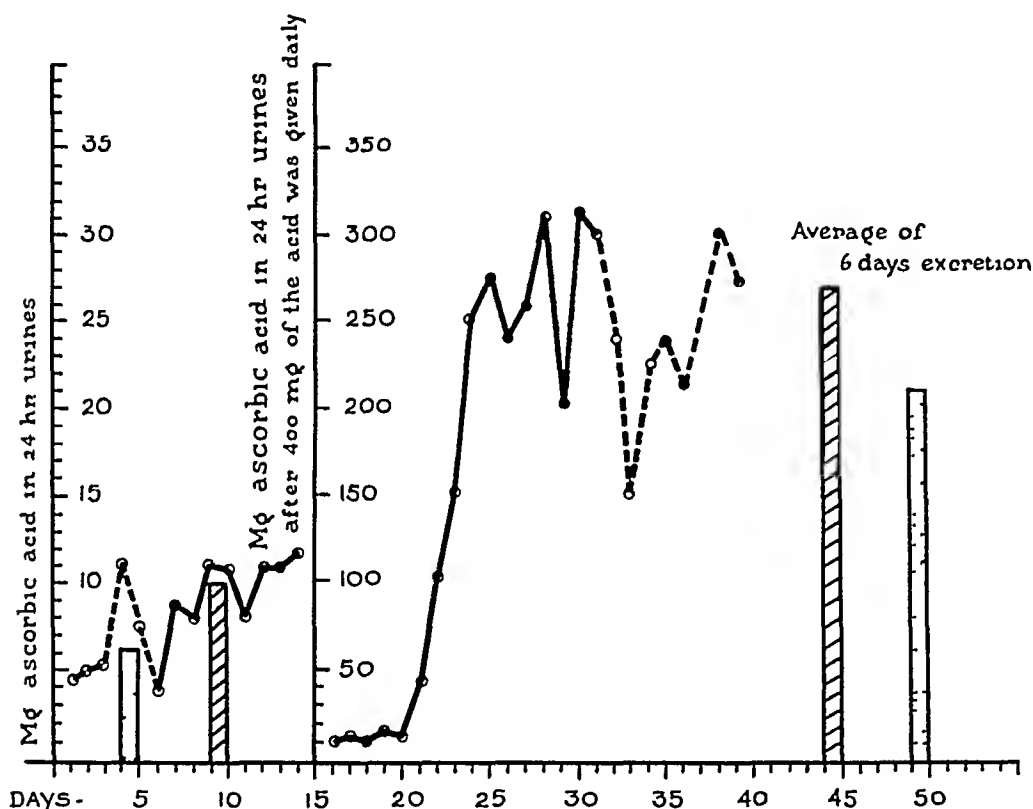


Chart 4—Relation of the excretion of ascorbic acid to the medication with alkali in a patient with peptic ulcer

At the right, under "Average of 6 days excretion," the cross-hatched column represents the excretion of ascorbic acid in a period when the subject (W. P.) received no alkalis, the stippled column, excretion in a period when the patient received 4 Gm of alkali every hour.

saturation" of the tissues with the aid of alkalis—and when this state was reached the ascorbic acid was again excreted in the previous greater amounts. Therefore, instead of interfering with the absorption of the vitamin, the medication seemed to aid the body in retaining greater amounts of it. Hawley and co-workers<sup>36</sup> found that patients kept on a

<sup>36</sup> Hawley, E. E., Frazer, J., Button, L., and Stephens, D. J. Effect of Ingestion of Acid and Alkali upon Amount of Vitamin C in Urine, *Proc. Soc. Exper. Biol. & Med.* **34**:218, 1936.



constant diet showed greater excretion of ascorbic acid when acid salts were administered than when alkaline salts were given

#### ASTHMA

It has been demonstrated by various workers<sup>37</sup> that the adrenal gland contains a larger concentration of ascorbic acid than any other organ in the body. Ordinarily the cortex of the gland has stronger reducing capacity than the medulla, but after anaphylactic shock, anger, ether or chloroform anesthesia or emotional reactions that entail an increase in the secretion of epinephrine, the reverse is found to be true<sup>38</sup>. These observations point to the possibility that ascorbic acid is connected intimately with the function of the adrenal gland, and probably it is active in the mechanism of the secretion of epinephrine.

A claim has also been made that vitamin C protects against sensitivity to arsphenamine,<sup>39</sup> but the lowering of the concentration of vitamin C in the blood has been considered by others<sup>40</sup> to be secondary to the reaction to arsphenamine. A claim has also been made that ascorbic acid may be a defense against anaphylactic shock, but this was denied by van Niekerk,<sup>41</sup> who showed that sensitized guinea pigs receiving large doses of vitamin C were unable to withstand anaphylactic shock any better than vitamin-C deficient controls.

Since epinephrine is so helpful in asthmatic attacks, we thought there might be some relation between this disease and ascorbic acid. Is the asthmatic patient unable to store the vitamin, with resultant malfunction of the adrenal gland because of the absence of this very important factor in the tissues? This question we set out to answer.

We studied 2 patients with clinical asthma of long duration who showed poor therapeutic response. One of these (S. P.) was malnourished and underweight because of severe restrictions on her diet due to her sensitivity to various foods. Her basal urinary excretion of ascorbic acid was low, 10 to 13 mg., and the concentration of the vitamin in the blood plasma was 0.46 mg. per hundred cubic centimeters. In spite of this we caused further depletion by putting her on a scorbutic diet for one week, both urine and blood showing a resultant drop in concentration of ascorbic acid. When she was given the 400 mg. of

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37 Bourne, G. The Role of Vitamin C in the Organism as Suggested by Its Cytology, *Physiol. Rev.* **16** 442, 1936.

38 Bourne, G. Vitamin C, *M. J. Australia* **1** 339, 1934, footnote 37.

39 Cormia, F. E. Experimental Arsphenamin Dermatitis. The Influence of Vitamin C in the Production of Arsphenamin Sensitiveness, *Canad. M. A. J.* **36** 392, 1937.

40 Friend, D. G., and Marquis, H. U. Arsphenamin Sensitivity and Vitamin C, *Am. J. Syph., Gonorr. & Ven. Dis.* **22** 239, 1938.

41 van Niekerk, J. Anaphylaxis and Vitamin C, *J. Allergy* **8** 446, 1937.

ascorbic acid daily, there was some slight increase immediately, but a peak did not occur until the fifth day, in other words, about 1,800 mg of vitamin was stored. Saturation occurred after a few more days, with excretion of over 300 mg daily. Her fasting blood plasma concentration did not rise above 1.38 mg per hundred cubic centimeters, which is slightly lower than the value for our controls. We thought this might conceivably have some effect on the syndrome, so we decided to give the patient some crystalline ascorbic acid intravenously. During one severe attack, occurring after the patient was saturated, we gave her 1,000 mg intravenously, but it had no effect on the attack, and epinephrine had to be administered.

The other patient showed evidence of good vitamin C nutrition both as to the concentration in the blood plasma and the amounts excreted in the urine and as to quick saturation, but his asthmatic attacks continued unabated. Since the concentration in the blood did not quite reach the optimal saturation level, we thought that this might be related to the

TABLE 4—*Centimic Concentration of Ascorbic Acid in Blood Plasma and in Ascitic Fluid*

Patient	Blood Plasma		Ascitic Fluid	
	Amount of Dye, Cc	Mg Ascorbic Acid per 100 Cc	Amount of Dye, Cc	Mg Ascorbic Acid per 100 Cc
C. A.	0.47	1.48	0.46	1.45
C. A.	0.40	1.23	0.59	1.2
M. D.	0.20	0.61	0.20	0.61
J. N.	0.20	0.61	0.19	0.59

repeated injections of epinephrine which these patients received. We were unable to demonstrate a depressing effect on the ascorbic acid in the blood by giving epinephrine hypodermically to another patient.

#### PORTAL CIRRHOSIS

Because of its size the liver is the largest storehouse for vitamin C in the body. The question arises whether in clinical conditions accompanied by widespread destruction of liver parenchyma there may not be inadequate storage of this vitamin. A patient with portal cirrhosis who had unquestionable hepatic damage was chosen. This patient had ascites, moderate jaundice, a reversal of the albumin-globulin ratio, and a small liver.

He was put on a vitamin C-free diet for eight days. Although the urinary excretion of the vitamin was close to 20 mg per twenty-four hours, the blood concentration was only 0.36 and 0.39 mg per hundred cubic centimeters. The high initial amount excreted is interpreted as due to interference of the bilirubinuria with the titration at these lower figures.

When the administration of the 400 mg doses of ascorbic acid began, no sharp rise in excretion occurred until the sixth day, during which time over 2,000 mg of the vitamin was retained. This is a usual finding in an exhausted patient, and proved that in spite of the destruction of liver parenchyma, storage of the vitamin was still possible. The excretion of the vitamin continued rising until a level compatible with normal was reached. At one time 290 mg and at another time 297 mg was excreted, lower levels were observed at other times. There are two reasons why a higher excretion was not maintained throughout. This patient had a low elevation of temperature every afternoon. Moreover, loss of ascitic fluid was a source of loss of ascorbic acid.

An additional interesting observation made by us in this case is that ascitic fluid, at least in portal cirrhosis, contains the same concentration of ascorbic acid as does blood plasma (table 4). We used the same method in both determinations. The storage of the vitamin in the ascitic fluid results in recovery of smaller amounts in the urine.

#### CONCLUSIONS

1 Persons normal from a dietary point of view show a prompt rise in urinary excretion and blood concentration of ascorbic acid, with rapid "saturation," when large doses are administered by mouth.

2 "Exhausted" patients show a delay in saturation, but their blood concentration rises above 1 mg per hundred cubic centimeters before a great rise in the urinary excretion occurs.

3 The diagnostic features of scurvy seem to be a lowered renal threshold for ascorbic acid, extreme depletion of the body stores and an unusual delay of saturation as evidenced by urinary excretion.

4 There seems to be increased utilization of ascorbic acid in diseases accompanied by increase in oxidative processes or in cellular proliferation, i. e., in (a) malignant tumor, (b) hyperthyroidism and (c) leukemia. This observation may be of interest from both a diagnostic and a therapeutic point of view.

5 Alkali medication does not interfere with absorption of ascorbic acid in cases of peptic ulcer. Treatment by "Sippy" diets when prolonged leads to depletion of stores of ascorbic acid.

6 Patients with clinical asthma show no abnormality of storage. Large doses of ascorbic acid given intravenously or by mouth have no ameliorating effect on the attacks.

7 The damage of the liver in portal cirrhosis does not interfere with storage of ascorbic acid. Ascitic fluid contains the same concentration of ascorbic acid as blood plasma.

# INCIDENCE OF PULMONARY AND EXTRA-PULMONARY TUBERCULOSIS IN ANTHRACITE COAL MINERS

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Pulmonary tuberculosis is a frequent complication of anthracosilicosis. A study made by the United States Public Health Service<sup>1</sup> in the anthracite region of Pennsylvania in 1934 showed that 20.4 per cent of miners and mine laborers over the age of 55 (i.e., those having the longest exposure to mine dusts) had clinical tuberculosis. A survey has just been completed at the White Haven Sanatorium<sup>2</sup> of the incidence of tuberculosis among anthracite miners coming to autopsy in the various institutions in Luzerne County. Of 541 cases in which autopsy was performed on miners, pulmonary tuberculosis was the principal cause of death in 21.3 per cent, whereas of 730 cases in which autopsy was performed on male nonminers of the same age during the same period in the same institutions tuberculosis was the cause of death in 8.9 per cent. In other words, pulmonary tuberculosis is more than twice as common in miners as in nonminers. In view of the frequency of pulmonary tuberculosis complicating anthracosilicosis, a study of the frequency with which extrapulmonary tuberculosis may occur in patients with the combined diseases should be of value.

Between May 1934 and May 1938 a complete postmortem examination was made at the White Haven Sanatorium of 50 patients with anthracosilicosis associated with pulmonary tuberculosis and of 84 patients with nonanthracosilicotic pulmonary tuberculosis. During approximately the same period laryngologic examinations were made by Dr. Joseph Donnelly<sup>3</sup> of 100 tuberculous miners and 265 tuberculous adult male nonminers. The data obtained form the basis for this study.

Of the 50 patients with anthracosilicosis 20 per cent had intestinal tuberculosis, while of the 84 with pulmonary tuberculosis not associated with anthracosilicosis, 51 per cent had intestinal tuberculosis.

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From the White Haven Sanatorium

Read at a meeting of the Laennec Society, Philadelphia, April 26, 1938

1 Special Bulletin 41, Commonwealth of Pennsylvania, Department of Labor and Industry, 1934

2 Charr, R., Cohen, A. C., and Bettag, O. L. Internat. Clin., to be published

3 Donnelly, J. Personal communication to the author

*Age*—Six patients with anthracosilicosis were below 30 years of age, of these, 4 (67 per cent) had intestinal tuberculosis. Fifty nonminers were below the age of 30, of these 29 (58 per cent) had intestinal tuberculosis. Of 44 tuberculous miners above the age of 30, 6 (14 per cent) had intestinal tuberculosis, of the 34 tuberculous nonminers, 14 (41 per cent) had intestinal tuberculosis.

*Extent of Anthracosilicosis*—Thirty-five per cent of the 20 patients with early or moderately advanced anthracosilicosis had intestinal tuberculosis, whereas only 10 per cent of the 30 patients with far advanced anthracosilicosis had involvement of the intestines (table 1).

*Type of Pulmonary Tuberculosis Complicating Anthracosilicosis*—Eleven (55 per cent) of the 20 patients with early or moderately advanced conditions had acute caseous lesions, and 9 (45 per cent) had fibrotic lesions. Of those having caseous lesions, 5 (45 per cent) showed intestinal tuberculosis, and of those having fibrotic lesions, 3

TABLE 1—Frequency of Intestinal Tuberculosis According to Degree of Anthracosilicosis

	Anthracosilicosis		
	Absent	Minimal or Moderately Advanced	Far Advanced
Number of patients	81	20	30
Number with intestinal tuberculosis	43	7	3
Percentage with intestinal tuberculosis	51	35	10

(33 per cent) had intestinal involvement. Of 30 patients with far advanced anthracosilicosis, 3 (10 per cent) had acute caseous lesions, while 27 (90 per cent) had fibrotic tuberculosis. One patient (33 per cent) in the group with caseous lesions and 1 (4 per cent) in the group with fibrotic lesions showed intestinal involvement. In only 3 of these patients was the pulmonary tuberculosis minimal, in all the rest it was far advanced, with cavitation.

*Laryngeal Tuberculosis*—During approximately the same period a study was made of 365 larynges, 100 of the subjects being miners and 265 being male nonminers. All examinations were made by the same laryngologist. Of the miners, 27 per cent had laryngeal tuberculosis; of the nonminers, 31 per cent had laryngeal tuberculosis. This difference becomes significant when it is considered that in the miners the condition was much more severe, 57 per cent of the miners and only 12 per cent of the nonminers died of tuberculosis in the sanatorium. Of the miners who died of tuberculosis, 33 per cent had laryngeal tuberculosis, whereas of the nonminers who died of tuberculosis, 59 per cent had laryngeal tuberculosis. Because the incidence of laryngeal tuberculosis is said to be different in different age groups, the age group in

which most of the miners were observed (30 to 49 years) was compared with the same age group for nonminers. Of the 33 miners who died of tuberculosis between the ages of 30 and 49 years, 33 per cent had tuberculous laryngitis, while of the 15 nonminers of the same age who died of tuberculosis, 47 per cent had tuberculous laryngitis.

*Tuberculosis of Other Organs*—Examination of the records of the necropsies previously mentioned for patients with extrapulmonary tuberculosis involving organs other than the larynx or the intestines did not provide enough cases of tuberculosis of any one organ to make comparisons between miners and nonminers significant. However, 32 per cent of 50 miners had such lesions, as against 46 per cent of 37 adult male nonminers (table 2).

TABLE 2—*Frequency of Extrapulmonary Tuberculosis in Men Dying of Far Advanced Pulmonary Tuberculosis*

	Intestines			Larynx			Other Extra pulmonary Organs		
	No of Patients	No with Tuberculosis	Percentage with Tuberculosis	No of Patients	No with Tuberculosis	Percentage with Tuberculosis	No of Patients	No with Tuberculosis	Percentage with Tuberculosis
Anthracosis Present	50	10	20	54	18	33	50	16	32
Absent	37	19	51	32	19	59	37	17	46

#### COMMENT

The prevalence of intestinal tuberculosis in association with ordinary pulmonary tuberculosis is well known, various investigators have observed it at necropsy in from 50 to 90 per cent of cases in which death was caused by tuberculosis.<sup>4</sup> Its relative infrequency as a complication of tuberculous anthracosis is striking.

It has been recognized that intestinal tuberculosis is commoner in young than in old tuberculous patients. This is also true of anthracosis associated with pulmonary tuberculosis, of miners above the age of 30, only 14 per cent had intestinal tuberculosis, whereas of the younger group, 67 per cent showed it. The reason appears to be that among the younger miners the degree of anthracosis was less and the pulmonary tuberculosis was more acute, resembling tuberculosis in nonminers. However, age per se does not appear to be the determining factor in the incidence of intestinal tuberculosis in miners, most of the miners with far advanced anthracosis were 30 years of age and older, and in this age group the miners showed a 14 per cent

<sup>4</sup> Rubin, E. H. *Am Rev Tuberc* **22** 184, 1930. Fishberg, M. *Pulmonary Tuberculosis*, ed. 4, Philadelphia, Lea & Febiger, 1932, vol. 2, p. 153.

incidence of intestinal tuberculosis, while the nonminers showed an incidence of 41 per cent

In combination with early or moderately advanced anthracosilicosis, intestinal tuberculosis occurred with nearly the same frequency as in combination with nonanthracosilicotic pulmonary tuberculosis. In association with these conditions pulmonary tuberculosis showed a definite tendency toward rapid spread and destruction. The amount of intestinal involvement, when this occurred, was great, often the entire length of the ileum and cecum and other parts of the large bowel were involved. In the presence of far advanced anthracosilicosis, tuberculosis of the intestines occurred rarely, when it did occur the lesions were, as a rule, few and not extensive (table 1).

It seems that anthracosilicosis favors the development of pulmonary tuberculosis. Sokoloff<sup>5</sup> found that the incidence of pulmonary tuberculosis increased in direct proportion to that of anthracosilicosis, and the previously mentioned report of the United States Public Health Service<sup>1</sup> emphasized the fact that the incidence of pulmonary tuberculosis is greatest among miners who have been longest exposed to mine dusts. The incidence of intestinal tuberculosis, on the contrary, is least among those who have the highest degree of anthracosilicosis.

The rarity of intestinal tuberculosis in the late stage of anthracosilicosis is probably due to the presence of pulmonary fibrosis and the customary chronicity of pulmonary tuberculosis in these patients, as observed by Landis.<sup>6</sup> When a cavity forms in the center of an anthracosilicotic mass it enlarges very slowly. Often such a cavity contains mucoid material having only a few tubercle bacilli or none, the wall of the cavity and the surrounding tissue when examined microscopically show few tubercle bacilli or none. Furthermore, the blood vessels in the anthracosilicotic mass and particularly in the neighborhood of the cavity always undergo extreme sclerosis, frequently followed by thrombosis. Blood vessels completely obliterated by fibrosis are frequently observed.<sup>7</sup> Such vascular changes tend to prevent the spread of tubercle bacilli.

The pathogenesis of secondary tuberculosis of the intestines is not clearly understood. The condition may be due to direct infection from swallowed sputum containing tubercle bacilli or to a spread through the lymphatic system or the blood stream. Animal experiments have not given convincing results.<sup>8</sup> It is easier to produce tuberculous enteritis in healthy animals by parenteral injection than by feeding tuberculous

5 Sokoloff, M. J. *Am Rev Tuberc* **34**:700, 1936.

6 Landis, H. R. M. *J Indust Hyg* **1** 117, 1919.

7 Charr, R., and Riddle, R. *Am J M Sc* **194** 502, 1937.

8 Maxwell, J. *Tubercle* **17** 337, 1936.

material, but the experimental work is not conclusive. In this study all patients with intestinal tuberculosis associated with either anthracosilicosis or pulmonary tuberculosis had sputum which repeatedly yielded bacteria and showed a high Gaffky grading, on the other hand, there were many patients with such sputum who had no intestinal lesions. Three of the 8 patients suffering from anthracosilicosis with intestinal involvement had tubercles in the kidneys as well, in these cases the mode of infection may have been through the circulatory system.

As to the symptoms of intestinal tuberculosis, it was interesting to note that in 5 cases of anthracosilicosis with tuberculosis of the intestines there was no complaint suggesting intestinal involvement. In 5 cases abdominal pain, tenderness in the right lower abdominal quadrant, diarrhea, nausea and vomiting were present from time to time either singly or together. Walsh<sup>9</sup> and also Boles and Gershon-Cohen<sup>10</sup> have observed that clinical symptoms and signs—abdominal pain, tenderness, diarrhea and rigidity—are of little value as diagnostic criteria. This has been substantiated in the present study. Repeatedly, symptoms characteristic of acute appendicitis were observed, but actually acute appendicitis is not commonly associated with pulmonary tuberculosis. Tuberculosis of the appendix is not uncommon, however, of the 53 patients with intestinal tuberculosis studied, 9 (17 per cent) had macroscopic ulcers of the appendix. The danger of perforation of the intestine is small, this complication having occurred in only 1 patient (2 per cent) of this series.

Patients with far advanced anthracosilicosis, with or without tuberculosis, frequently complain of anorexia, vague abdominal discomfort, flatulence and diarrhea alternating with constipation. These symptoms are perhaps due to chronic passive congestion of the gastrointestinal tract secondary to myocardial weakness, which is a common occurrence in cases of anthracosilicosis.

#### SUMMARY AND CONCLUSIONS

Pulmonary tuberculosis is more frequent in anthracite miners than in nonminers of the same age and sex.

Tuberculosis of the intestines, the larynx and other extrapulmonary organs is, however, less frequent in miners than in nonminers.

In the majority of cases of intestinal tuberculosis associated with anthracosilicosis there were no symptoms referable to the gastrointes-

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9 Walsh, J. New York M J 90 100, 1909

10 Boles, R. S., and Gershon-Cohen, J. Intestinal Tuberculosis Pathologic and Roentgenologic Observations, J A M A 103 1841 (Dec 15) 1934



tinal tract. Pain, tenderness and diarrhea, though sometimes present, could not be depended on as diagnostic criteria.

The relative infrequency of extrapulmonary tuberculosis in the presence of anthracosilicosis is due to the extensive fibrosis and relative avascularity of the lungs and the chronicity of the pulmonary tuberculosis usually present in these patients. These factors apparently tend to prevent the spread of tuberculous infection to other parts of the body.

Dr. Joseph Walsh gave permission for the use of the material presented in this study.

# RELATION OF HEREDITARY PATTERN TO CLINICAL SEVERITY AS ILLUSTRATED BY PERONEAL ATROPHY

WILLIAM ALLAN, M D

CHARLOTTE, N C

Field work in the inheritance of human disease has brought to light two striking phenomena

First, in regard to many of the diseases due to unit traits, that is, conditioned by a single defective gene, a wide survey of 50 to 100 families possessing such a trait usually shows a triple pattern of inheritance dominant, sex-linked recessive and simple recessive

How general this rule is in human, animal or plant genetics is not known, nor is it obvious why the same trait should be dominant in 1 family and recessive in a second and in a third side the sex chromosomes down the generations, becoming manifest only in the males

The second phenomenon, a corollary of the first, is that the pattern of inheritance determines the age of onset and the clinical severity of various morbid unitary traits, as may be seen by a study of peroneal atrophy (Charcot-Marie-Tooth type)

Lenz<sup>1</sup> repeatedly called attention to the mildness of dominant traits and by way of explanation said "In the case of dominant heredity, severe and rapidly progressing forms would not be able to maintain themselves in existence" This idea of the survival of the fittest only might well be true for muscular dystrophy should the children not survive to the reproductive age, but the same explanation cannot hold for many other unitary traits which are nonlethal even when severe, such as retinitis pigmentosa and peroneal atrophy A much more rational explanation seems to be that the behavior of the genes determines the age of onset and the clinical severity of the disease

Last year I showed<sup>2</sup> that when retinitis pigmentosa is dominant, those affected are only half blind, night blind or "moon-eyed," the age of onset being between 25 and 40 years, and the severity rarely pro-

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1 Baur, E, Fischer, E, and Lenz, F Human Heredity, New York, The Macmillan Company, 1931, chap 9, pp 407 and 410

2 Allan, W Eugenic Significance of Retinitis Pigmentosa, Arch Ophth 18:938 (Dec) 1937

gressing to total blindness even after the age of 60 years, when the condition is sex-linked recessive, the age of onset is in the second or third decade, and complete blindness supervenes between the ages of 40 and 50, when it is simple recessive, sight begins to fail in the first decade, and in such cases children become stone blind before they are 20

The same rule, or law, holds in regard to peroneal atrophy. The afflicted members of the family in which peroneal atrophy is dominant (fig 1) notice beginning disability about the age of 30 but are able to plough their fields and pick cotton past the age of 70. The atrophy is moderate, or there may be only pes cavus.

When peroneal atrophy is sex-linked recessive (fig 2), the boys notice atrophy about the middle of the second decade and by the time they are 25 are too disabled for such occupations as watchmaking and bookkeeping, are on crutches or are bedridden.

When it is a simple recessive trait (fig 3), peroneal atrophy begins before the age of 8 years, and in the second decade its victims become hopeless cripples.

The explanation seems to be this. Those in whom the trait is dominant, who are all heterozygous in case of these uncommon diseases, receive one defective gene from the affected parent and one normal gene from the unaffected parent, such a pair of genes, half good and half bad, causes half blindness or half crippling with late onset.

The boys with a sex-linked recessive trait, of course, receive one defective gene from their mother, without any corresponding normal gene on the chromosome they receive from their father, and the trait is correspondingly more severe, with an earlier onset.

When the trait is simple recessive, each parent supplying a defective gene, there is nothing to ameliorate the intensity of the disease, and it is very severe, with an early onset. This behavior of the genes explains the relation of hereditary pattern to clinical severity and age of onset.

These fundamental laws of the genetics of human pathology have some highly practical bearings on voluntary negative eugenics. When dominant, these diseases may not be severe enough to impel the afflicted parents to forswear propagation. However, when sex-linked recessive or simple recessive, the traits are disastrous enough to make voluntary birth control a welcome discipline in these families whenever the parents are properly informed. The simplicity with which a program for negative eugenics can be instituted and carried out has been repeatedly emphasized<sup>3</sup> and need not be gone into here. Suffice it to say that

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3 Allan, W. The Relationship of Eugenics to Public Health, *Eugenical News* 21:73 (July) 1936, *Medicine's Need of Eugenics*, *South Med & Surg* 98:416 (Aug) 1936.

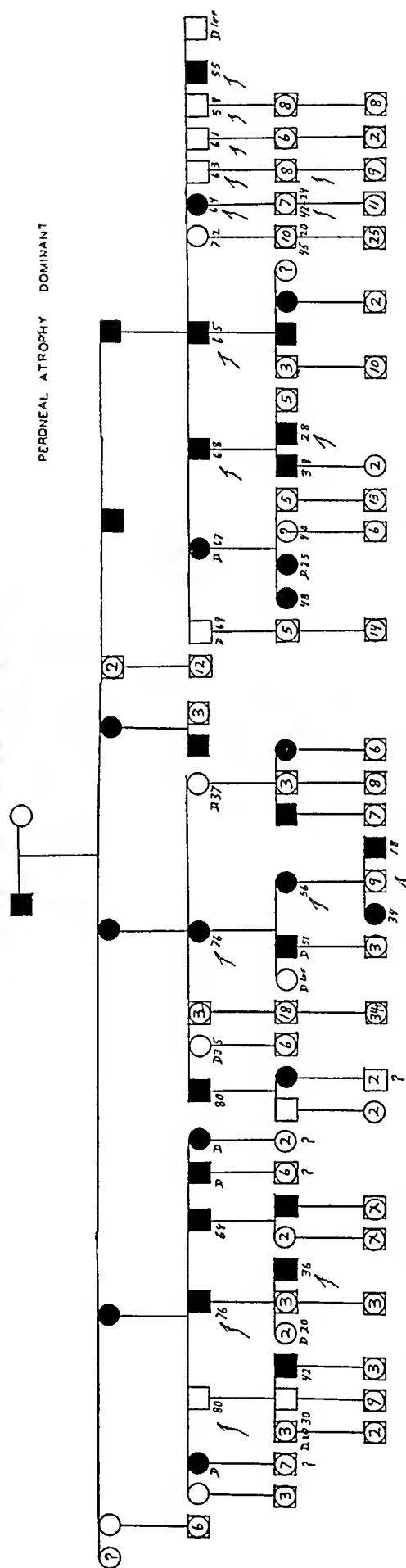


Fig 1—Pedigree 1 and G III 26 In all pedigrees squares denote men, circles, women, circles within squares, both sexes, black, peroneal atrophy, white, normal, figures within symbols, number of persons, age of person or of oldest of group The arabic figures following the designation of the generation indicate the place of each symbol in its generation, counting from left to right Fingers point to those whom I examined Circles or squares containing smaller circles or squares within them in pedigrees 2 and 3 denote carriers of the trait

many of the diseases that wreck childhood will be voluntarily suppressed or eliminated whenever, after a study of the hereditary pattern in the individual family, those concerned are warned as to what is in store for their children

#### PEDIGREE 1

This pedigree (fig 1), which shows peroneal atrophy as a dominant unit trait, was started with G III 26, whose photograph accompanies the chart. He began to notice trouble with his ankles at the age of 25 years, at 55 he had marked atrophy of the muscles below the knees and elbows but got around well.

It was known by many of his generation that the grandfather, G I 1, had badly crippled feet. G II 1 married early and moved to Missouri, and nothing more is known of her. G II 2 and her 6 children had no crippling. G II 3 married her second cousin (on the mother's side of the family), who was not reported as crippled, however, she and 5 of her 7 children had peroneal atrophy. Her oldest daughter, G III 2, married and moved to another county early in life, but the relatives stated that the family had no atrophy. The other 2 girls in this sibship, G III 3 and 8, both manifested atrophy after typhoid in the early twenties, but the condition of their children is not known. I found G III 4 shucking corn at the age of 80 and failed to detect atrophy or foot drop, one of his sons was said to walk on the outside of his feet and to be unable to plow, but as this man was away at a corn husking I failed to see him. Apparently the trait skipped a generation here. Whether the high proportion of affected children in this sibship was a matter of chance or was due to the kinship of the parents is uncertain. The next 2 sons, G III 5 and 6, both had foot drop with some atrophy of the hands, and each had an affected son. I found G III 5 mending harness, he had mild atrophy of the hands and foot drop. The affected son G IV 8 was plowing. He had pes cavus and could not avert his feet. The last son, G III 7, was severely crippled, but I could get no report on his 6 children. The fourth child, G II 4, and 2 of her 7 children, G III 9 and 12, had atrophy. G III 9's daughter, G IV 14, had atrophy, but the condition of her 2 sons was not known. G III 12, when seen at the age of 76, had marked atrophy of both hands and feet, her son, G IV 18, had peroneal atrophy, but as his oldest child was only 28 at the time of investigation it was too early to know what will happen to his children.

G IV 19 had marked outward rotation of the right ankle, with peroneal atrophy coming on a few years before she was seen. Two (G V 11 and 13) of her 11 children were showing the early signs of peroneal atrophy.

G II 4 lost 2 daughters when they were about 35 years old, there was no atrophy in the 6 children of one (G III 10), but 2 (G IV 20 and 22) of the 5 children of the other (G III 13) had crippled feet. As G III 13 herself was reported not to have had atrophy, either the trait skipped a generation, or she died before it became manifest.

The next daughter, G II 5, and 1 of her 4 children are reported to have had the family disability.

The next 2 sons, G II 6, and the 6 children of each were free from atrophy. The third son, G II 7, was severely crippled and died childless in old age. The last son, G II 8, was moderately crippled. His oldest son, G III 17, and this son's 5 children were all free from atrophy. The second child, G III 18, and 2 of her 8 children, G IV 24 and 25, had atrophy, while the status of a third child, G IV 26, was doubtful.

I examined G III 19 and 1 of his affected sons, G IV 29, neither of whom was badly disabled. The other son, G IV 28, was a guard at a convict camp, which indicates that his atrophy was not severe. All 3 noticed beginning lameness at about the age of 25.

I examined G III 20 when he was 65 years old and found him cutting wood with difficulty. He first noticed beginning lameness at 20. His affected son, G IV 32, had atrophy of the hands, while the affected daughter, G IV 33, had involvement of both hands and feet. The condition of one daughter, G IV 34, was uncertain, since she married early, moved away and had not kept in touch with her family. None of the grandchildren of G III 18, 19 and 20 was old enough to show the trait.

The fifth child, G III 21, and her 10 children escaped the family affliction. I saw that the sixth child, G III 22, had typical atrophy of both hands and feet, but none of her 7 children, ranging in age from 42 to 24 years, had as yet manifested atrophy. Neither G III 23 nor any of his 8 children had peroneal atrophy, but 3 of these children inherited lobster claw hands from their mother's family.

The eighth child, G III 24, and his 6 children as well as the ninth child, G III 25, and his 8 children were all free from atrophy. The tenth child, G III 26, who has already been described, had no children. G III 27 died in infancy.

Peroneal atrophy in this family begins any time between the ages of 25 and 50 and varies from a light to a moderately severe handicap in the life of these farmers and their wives. In some cases only the feet are involved, in others, the arms and hands later become atrophied. Although occupations that require much walking, such as plowing and cooking, may be interfered with, none of the family has ever quit working at the occupations which require less locomotion.

Since peroneal atrophy is inherited here as a simple dominant trait, coming on late and never causing total disability, the affected members of this family look on it as a handicap rather than a disaster and probably would not give up having children, even if warned that half their children will be similarly affected.

#### PEDIGREE 2

In 1936 the young man G IV 43, aged 25 years, whose photograph accompanies this pedigree (fig 2), was referred to me because his hands were too severely disabled to carry on his business of watchmaking. He wore braces below the knees. The disability was typical hereditary peroneal atrophy. With this man's help I combed Cabarrus County, working out the family history and visiting the relatives. His great-grandmother, G I 4, brought the trait into the family, since 2 of her brothers, G I 5 and 9, had it. Another brother, G I 8, married a wife, probably a kinswoman, who as part of her dower also brought along peroneal atrophy, passing it down in the collateral branches G III 29 and 30 and G IV 56 and 58. Although I have visited the 4 living members of the second generation, aged 77 to 92, this wife's name has been lost. A glance at the chart shows the pattern here to be sex-linked recessive, with 1 instance in a woman, G III 30, of incomplete recessiveness.

The great-grandmother's oldest son, G II 1, was severely crippled, and his two daughters, G III 1 and 4, were of course transmitters. I visited the older

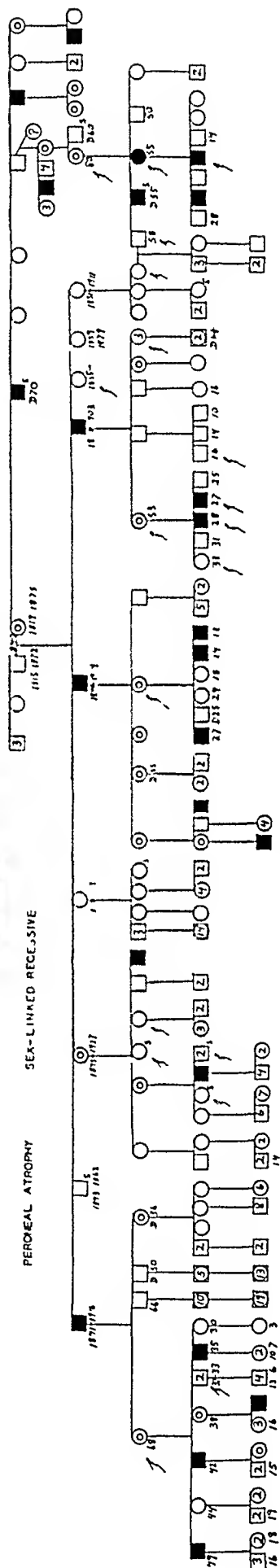


Fig 2—Pedigree 2 and G IV 43

of these daughters, aged 68, who reported that 3 of her 5 sons, G IV 1, 3 and 6, were badly crippled, of her 3 daughters (G IV 2, 4 and 7), 1 (G IV 2) had 2 sons, G V 3, who escaped, 1 (G IV 4) passed the trait to her only son, G V 8, and 1 (G IV 7) had no sons. The other daughter of G II 1 died at 36, leaving 2 normal boys, G IV 10 and 3 girls, of whom 1 (G IV 11) was single, 1 (G IV 12) had 8 normal boys and 1 (G IV 13) had only girls.

G I 4's second child, a son killed in the Civil War, presumably was normal. Her third child (G II 3) was a carrier, passing the trait to 1 (G III 10) of her 2 boys. Of G II 3's 4 daughters, 3 married, the oldest (G III 5) had 1 normal boy (G IV 14) and 1 daughter (G IV 15), whose sons were too young for one to know about their inheritance.

G III 6, the second daughter, was a carrier, 1 (G IV 18) of her 3 boys being affected, her only married daughter (G IV 16) had 6 boys, all normal when investigated.

G III 8 had 2 normal boys and was probably not a carrier.

G I 4's fourth child (G II 4) was probably normal, as her 3 boys (G III 11) were normal as well as the 2 sons (G IV 26) of her daughter.

G I 4's fifth child (G II 5) was only moderately crippled, but his 4 grandsons and his great-grandson showed the severity usually seen when this trait is inherited as a sex-linked recessive.

G II 5's oldest daughter (G III 15) had 2 sons, 1 of whom was crippled (G IV 29), and 1 daughter (G IV 27), who passed the trait to her only son (G V 23). The second daughter (G III 16) had 2 sons, who by chance escaped atrophy. The third daughter (G III 17) was single, and the fourth daughter (G III 18), whom I visited, passed crippling on to 3 (G IV 32, 36 and 37) of her 4 boys.

G II 6 was severely crippled. The elder of his 2 boys (G III 21) was reported to have had foot drop at the age of 16, but after wearing braces day and night for some time he recovered entirely, what this lesion was is unknown, as the man was a scoutmaster and showed no signs of peroneal atrophy when this study was made.

G II 6's oldest daughter (G III 20) had 2 sons (G IV 42 and 43), who began to have difficulty in walking when about 17 years old, by the time they were 25 both had to give up their occupations, bookkeeping and watchmaking, respectively. The only sister in the fraternity was sterilized at her own request. The other 4 daughters (G III 23 and 24) of G II 6 had no living sons, and the only living daughter (G IV 49) applied for information on birth control before her recent marriage.

G II 7 was unmarried and the keeper of the family archives at the age of 82 years, G II 8 died single at the age of 20.

G II 9 was probably normal. She had 3 daughters, the oldest (G III 27) having 3 normal boys (G IV 53), the next (G III 25) having no children and the youngest (G III 26) having 2 normal boys.

In the second generation, 7 and 10, as well as the husband of 3 and the wife of 6, were still living at ages ranging from 78 to 93. It was common knowledge that G I 5 was a crippled old bachelor. Another brother, G I 9, was reported to have been crippled, his daughters dying without issue. One sister, G I 10, left 2 normal sons who died without issue. G I 6 left no children, and G I 7 married and moved to Illinois about a century ago. Another sister (G I 11) had a crippled son. G I 4 had a niece (the mother of G II 10) who evidently transmitted peroneal atrophy to the collateral branch descending from G II 10, whose father was normal. The name of this niece's mother was lost, and the relation of her father to G I 4 was somewhat uncertain.



G II 10's oldest son (G III 28) married his kinswoman (G III 27), probably a second cousin once removed, but they had normal children and grandchildren. The second son (G III 29) was crippled and died single. The next child (G III 30), a woman of 55 years, whom I examined, had the typical atrophy of arms and hands and could not doisiflex or evert her feet, although the muscles of the calf were good. This is evidently an example of incomplete recessiveness. Two

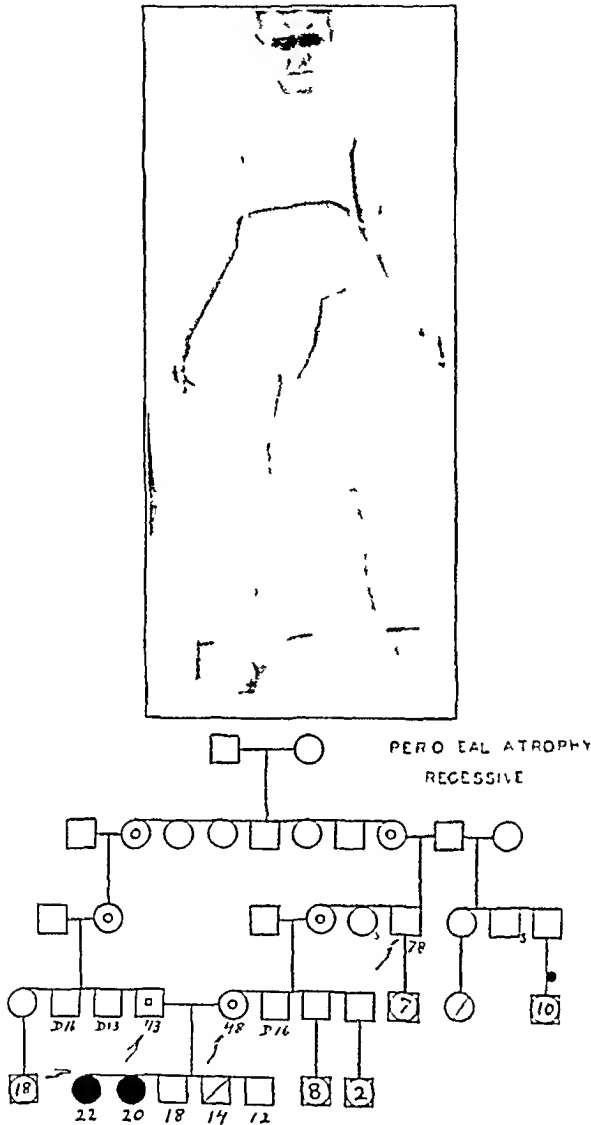


Fig 3—Pedigree 3 and GV 3

(G IV 56 and 58) of this woman's 5 sons had typical peroneal atrophy. G II 10's third son (G III 31) was normal, and her other daughter (G II 32) had 2 normal sons (G IV 62).

In the first three generations of this family the majority were severely crippled, but a few continued farming throughout life. In the last two generations the age of onset has been in the second decade,

and severe disability has supervened within ten or fifteen years. The hereditary pattern is sex-linked recessive, the defective gene being in the x chromosome in the crippled man, all of his daughters receive one of these chromosomes and are carriers of the trait, passing it on to half of their sons and daughters.

#### PEDIGREE 3

Last spring the North Carolina Orthopedic Hospital gave me the names and photographs of 8 young girls afflicted with peroneal atrophy. These patients came from 6 separate families, and as in each family the parents were normal it was evident that the hereditary pattern must be simple recessive. So far 4 of these families have been investigated, and, as was to be expected, in each instance the parents were cousins, pedigree 3 (fig 3), from Cabarrus County, pertains to the first of the families visited. The 2 girls G V 2 and 3, now aged 22 and 20 years, are severely crippled. Atrophy of the forearms and of the legs below the knees is extreme, the older girl began to have trouble walking at 3, the younger at 5. The photograph in figure 3 shows G V 3 at the age of 13. The parents, G IV 4 and 5, were normal but knew nothing about their family histories except that they had grandmothers with the same surname. However, they sent me to the wife's uncle, G III 6, aged 78, in another county, who gave me a much more extensive account of the first three generations than appears in the pedigree. Since 1800 there had been no other examples of peroneal atrophy within his knowledge. The parents of these children are second cousins, as will be seen from the chart.

This pedigree and the photograph illustrate the early onset and disastrous result of the disease when it is inherited as a simple recessive trait.

# CLINICAL RECOGNITION OF TUBERCULOSIS OF THE MAJOR BRONCHI

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Recognition of tuberculous disease of the trachea and the major bronchi is a recent achievement in clinical diagnosis. Although it is easy to understand why older clinicians, unaided by the roentgen film and the bronchoscope, did not suspect the existence of bronchial tuberculosis, it is not clear why pathologists failed to discover the changes characteristic of the condition at autopsy. Textbooks on pathology have been strangely silent with respect to this condition, which is now frequently reported from clinical sources.

With respect to the clinical features of bronchial tuberculosis, until recently references in the literature have been meager and have usually comprised reports of single cases, such as those by Korol,<sup>1</sup> Neumann,<sup>2</sup> McConkey,<sup>3</sup> Crimm and Strayer,<sup>4</sup> Fleischner<sup>5</sup> and Sanes and Smith.<sup>6</sup> In these cases the diagnosis, although clinically suspected, was proved only by autopsy.

Progress in the diagnosis of bronchial tuberculosis and allied conditions has run parallel with the use of the bronchoscope and of bronchographic examination. The prejudice of physicians against instrumentation of the bronchi in tuberculous patients has now been overcome, and the widespread use of the bronchoscope has brought to light the existence of bronchial lesions in an unexpectedly large number of patients. Begin-

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From the Tuberculosis Division of the Montefiore Hospital for Chronic Diseases.

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3 McConkey, M. Occlusion of Trachea and Bronchi by a Tuberculous Process Complicating Pulmonary Tuberculosis, *Am Rev Tuberc* **30** 307, 1934.

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5 Fleischner, F. Die tuberkulose Bronchostenose und ihre Unterscheidung vom Bronchuscarcinom, *Beitr z Klin d Tuberk* **87** 553, 1936.

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ing in 1928, sporadic examinations of the bronchi were made by various observers, among whom may be mentioned Sproull<sup>7</sup> and Schonwald,<sup>8</sup> who were able by such examinations to confirm for the first time the clinical diagnosis of bronchial disease. Since then reports of bronchial and tracheal lesions in tuberculosis have rapidly multiplied. Careful clinical and bronchoscopic correlations have rounded out a clinical picture of this condition which is gradually being fitted into the larger panorama of tuberculous disease of the respiratory organs. Many observers have contributed to this work. The first comprehensive attempt to incorporate bronchial tuberculosis into the general framework of tuberculosis of the lungs was made by Eloesser,<sup>9</sup> who in 1934 published in a monograph a series of cases in which the condition was clinically diagnosed and the diagnosis proved bronchoscopically. In the same year Myerson<sup>10</sup> reported bronchoscopic examinations in 60 cases of tuberculosis. Since then reports of series of cases have been made by Epstein and Ornstein,<sup>11</sup> Myerson,<sup>12</sup> Phelps,<sup>13</sup> Samson, Barnwell, Littig and Bugher,<sup>14</sup> Cohen and Higgins,<sup>15</sup> Ornstein and Epstein,<sup>16</sup> Kernan,<sup>17</sup> Sandler,<sup>18</sup> and Warren, Hammond and Tuttle,<sup>19</sup> Single cases have been reported by Werner,<sup>20</sup> Ballou<sup>21</sup> and Vinson.<sup>22</sup>

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8 Schonwald, P. Tuberculous Granuloma of the Bronchus, *Am Rev Tuberc* **18** 425, 1928

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10 Myerson, M. C. Bronchoscopy in Tuberculosis, *Ann Otol, Rhin & Laryng* **43** 1139, 1934

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12 Myerson, M. C. The Value of Bronchoscopy in Pulmonary Tuberculosis, *Quart Bull, Sea View Hosp* **1** 261, 1936

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17 Kernan, J. D. Tuberculosis of the Trachea and Main Bronchi, *Ann Otol, Rhin & Laryng* **47** 777, 1937

18 Sandler, E. Einige Falle von Stenosen der grosseren Bronchien bei Lungentuberkulose, *Acta tuberc Scandinav* **12** 1, 1938

19 Warren, W., Hammond, A. E., and Tuttle, W. M. The Diagnosis and Treatment of Tuberculous Tracheobronchitis, *Am Rev Tuberc* **37** 315, 1938

## PATHOGENESIS

The manner in which the bronchi become involved in the tuberculous process is somewhat obscure. It is safe to say that isolated tuberculosis of the bronchus unassociated with older disease in the lung or in the adjacent lymph nodes does not occur. Infection of the trachea and bronchi is always secondary to some previously existing focus of tuberculosis in the chest. One of these foci has long been recognized, especially by pediatricians, who are familiar with the fatal consequences of erosion of the bronchi by adjacent caseous lymph nodes. Scobie<sup>20</sup> in 1934 reviewed this subject and collected reports of 94 cases, in only 19 of which recovery occurred. In adults the extension of tuberculosis from caseous lymph nodes to the bronchi is much less common. Whether the lymph nodes of adults are less caseous and more calcified than those of children or the adult bronchial tissue is more resistant, the fact remains that mechanical compression of the bronchi is more likely to occur from these adjacent caseous lymph nodes than is ulceration.

The usual source of tuberculous infection of a bronchus is an open pulmonary tuberculous lesion lying peripheral to it, and it is logical to presume that the bacilli are implanted on the mucous membrane in the same way in which they are implanted in the larynx in cases of tuberculous laryngitis. It is not plausible to assume, as some authors have done,<sup>24</sup> that infection occurs by contiguity from tuberculous disease of the circumjacent lung. The most extensive bronchial disease is usually found in the larger tubes at the root of the lung, in a situation where the lung tissue is relatively uninvolved. The bronchi may also be involved, as is the larynx, in any hematogenous tuberculous infection, but it is likely that the tubercles so formed play little or no role clinically, we have recently observed a case of protracted miliar tuberculosis in which the mucosa of the lower portion of the trachea and one of the major bronchi were studded with tubercles.

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## PATHOLOGIC PICTURE

The pathologic character of tuberculous lesions of the trachea and bronchi warrants no detailed description here, as it differs little from that of tuberculous lesions elsewhere in the body. Tubercle formation is followed by caseation and ulceration as elsewhere, and the bronchoscope commonly discloses masses of granulation tissue, which often conceal underlying caseous or simple ulcerations. Important consequences result from penetration of the disease through the wall of the bronchus, with destruction of the cartilage. When this has occurred the bronchus can no longer maintain the patency of its lumen, and it gradually undergoes fibrous stricture with greater or less stenosis. Many of the clinical symptoms result from this narrowing of the bronchus with its mechanical effects on the lung tissue distal to it. Although physicians have become familiar with these changes through bronchoscopic studies, it must be remembered that the bronchoscope is limited in its scope by the small caliber of all but the larger bronchi. For this reason one is often in ignorance of tuberculous bronchial lesions which lie distal to an area narrowed by fibrous stricture or obstructed by granulations. In order to obtain a complete picture of the pathologic process it is necessary at times to resort to bronchographic examination, by means of which a considerable length of bronchus beyond the point of narrowing may be seen to be involved. In our experience bronchial stenosis associated with tuberculosis is never complete, although the cicatrized walls may be in apposition, a tiny lumen remains, through which secretions can find their way. One cannot, therefore, depend on the pathologic closure of a bronchus to prevent the spread of infection from the diseased lung to which it is tributary.

If one may judge from recent bronchoscopic reports, tuberculous lesions of the bronchi are far from rare, and it is likely that the routine examination of tuberculous patients would reveal a considerable number. This is indicated from the reports of Warren, Hammond and Tuttle,<sup>19</sup> who found 13 per cent of bronchial lesions in 90 cases in which bronchoscopic examination was done previous to thoracoplasty. In a series of 108 cases in which there were symptoms of bronchial disease, positive findings were obtained in 54 per cent. Recent autopsy studies have also shown the great frequency of bronchial lesions. Bugher, Littig and Culp<sup>25</sup> found such lesions in 33.6 per cent of 122 patients who died of tuberculosis. Even greater percentages are given by McConkey and Greenberg<sup>26</sup> who observed ulcerations in 43 of 53 autopsies.

25 Bugher, J. C., Littig, J., and Culp, J. Tuberculous Tracheobronchitis, *Am J M Sc* **193** 515, 1937.

26 McConkey, M., and Greenberg, S. Persistent Rhonchi in the Diagnosis of Bronchial Stenosis Complicating Pulmonary Tuberculosis, *Tr Am Climat & Clin A* **50** 218, 1934.

Since February 1935, bronchoscopic examination of all patients presenting clinical evidence of tuberculous lesions of the major bronchi has been done at the Montefiore Hospital. Twenty cases in which the clinical diagnosis was confirmed by bronchoscopic examination and in 3 of which it was also confirmed by postmortem examination are reported.

#### REPORT OF CASES

CASE 1—H. H., a man aged 58, had tuberculosis of the upper lobe of the right lung. Artificial pneumothorax was induced, with resultant selective collapse. After this, smears of the sputum failed to reveal tubercle bacilli. Eighteen months later symptoms recurred and the sputum again contained tubercle bacilli. The patient came under our observation ten months later.

On being questioned, he recalled having noted wheezing arising from beneath the sternum, commencing at about the time smears showed tubercle bacilli in the sputum. Examination showed pneumothorax on the right with selective collapse of the upper lobe, no cavities or infiltrations were seen in either lung. The trachea and the heart were in the midline.

Bronchoscopic study showed an ulceration about 1 cm. in diameter on the mesial wall of the right main bronchus, in the posterolateral branch of the bronchus to the lower lobe there was a sloughing whitish multilobular mass attached to the anterior wall. The ulcer was treated with a 35 per cent solution of silver nitrate, after which the sputum became free of tubercle bacilli, remaining so for the following five months of observation. Bronchoscopic study four months after treatment showed a depressed white scar on the mesial wall of the right main bronchus.

CASE 2—C. S., a woman aged 25, was admitted to the Montefiore Hospital in March 1937, with pulmonary tuberculosis of four years' duration. A roentgenogram showed a cavity in the upper lobe of the right lung, for which pneumothorax had been induced, without success. There were some healed infiltrations in the apex of the left lung. Smears of the sputum showed tubercle bacilli. A two stage thoracoplasty with removal of seven ribs and liberation of the apex (method of Semb) was done. The patient improved clinically, but the sputum continued intermittently to yield tubercle bacilli. She was admitted to the Mount Sinai Hospital in February 1938. A roentgenogram showed a slit in the upper lobe of the right lung, suggestive of a cavity, but a bronchogram revealed no excavation. On bronchoscopic study granulation tissue was found in the bronchus to the upper lobe of the right lung, on microscopic examination this tissue proved to be tuberculous. After a revision operation no suspicion of cavity remained, but the sputum still intermittently contained tubercle bacilli.

CASE 3—S. P., a woman aged 41, had pulmonary tuberculosis in 1928 (fig. 1 A). For the next nine years she had several exacerbations and remissions, with involvement first of the left lung, then of the right, and was a patient in several institutions. In November 1935 she first began to complain of wheezing in the left side of the chest, and a high-pitched rhonchus was heard. Examination in November 1937 revealed a loud wheeze which could be heard at a distance and which was localized to the left side of the chest. The patient was dyspneic on the slightest exertion. Breath sounds over the lower lobe of the left lung were distant, and a rhonchus was heard over the entire left lung. There was no evidence of cardiovascular disease. Smears of the sputum did not reveal tubercle bacilli. A roentgenogram showed a few calcific shadows in the lower lobe of the left lung but no significant infiltrations or cavities. In the hilus of the left lung there was a mass

which had gradually grown in intensity and size since the first film was taken in 1928 (fig 1 *B*) Bronchoscopic examination showed the lumen of the left main bronchus to be narrowed to about 60 per cent of its normal caliber by a thin ledge on the anterior and right walls, the bronchus to the lower lobe was narrowed 50 per cent by a circular constriction of the wall A bronchogram (fig 1 *C*) showed two strictures of the left main bronchus After a period of observation the patient was discharged unimproved

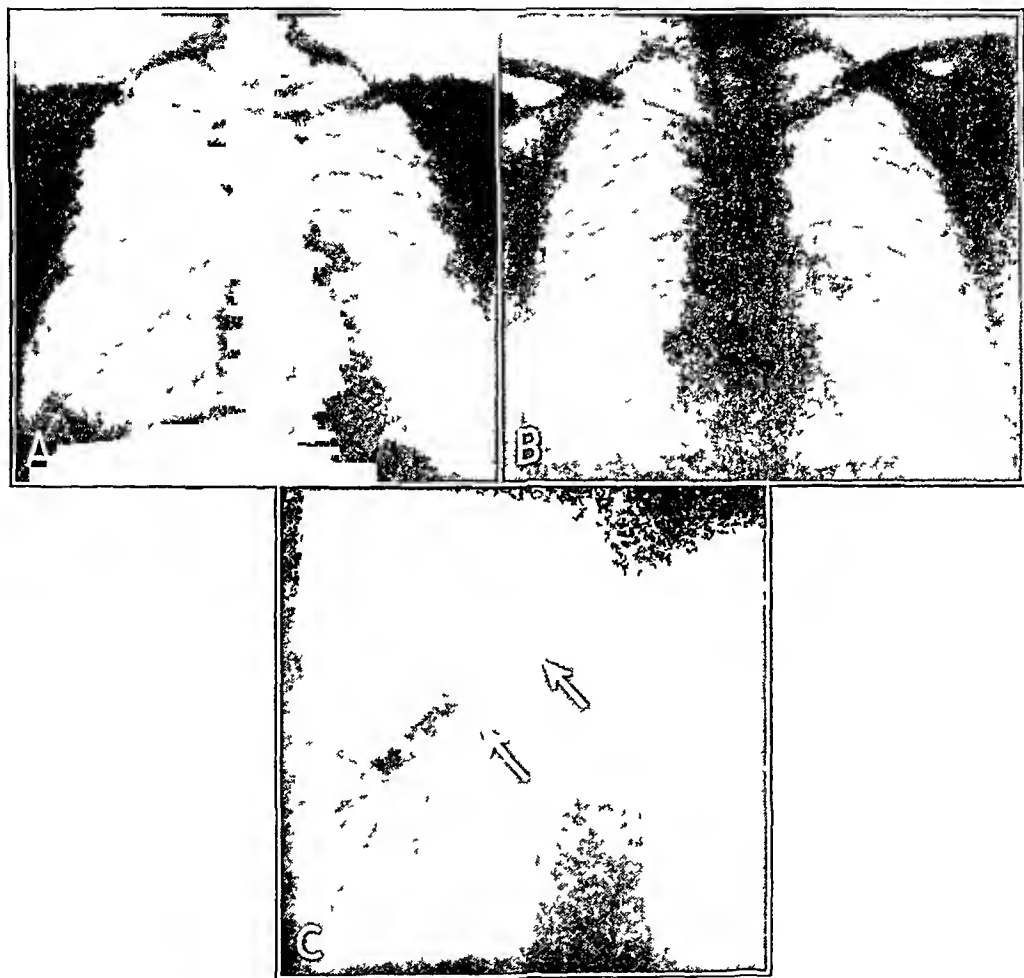


Fig 1 (case 3) —*A*, roentgenogram taken in 1928 at the onset of the disease *B*, roentgenogram taken in 1937 Note the increase in the size and intensity of the shadow in the left hilus and the absence of significant cavities or infiltrations *C*, bronchogram taken in 1937, showing strictures partially occluding the left main bronchus (photograph reversed)

CASE 4—*B N*, a woman aged 24, had suffered from “asthma” for many years She would get attacks of wheezing and suffocation, which were never relieved by injections of epinephrine hydrochloride She began to cough in 1930, and tuberculosis of the upper lobe of the left lung was found in 1931 Pneumothorax was induced, but a satisfactory collapse was not obtained and the procedure was abandoned Despite the pneumothorax, the heart and trachea were drawn to the left (fig 2 *A*) The intrapleural pressure was unusually low (high negative) The patient’s physician suspected an intrabronchial obstruction at this time



On admission to the hospital in January 1936 the patient still complained of intermittent wheezing. She suffered from severe attacks of choking, during which she became almost asphyxiated, lying on the right side provoked these attacks. Examination showed a large hydropneumothorax on the left, with sterile fluid, the trachea and heart were drawn to the left. Bronchoscopic examination showed the trachea to be narrowed at its lower portion, the left main bronchus was completely occluded, except for a small lumen about 2 mm in diameter, by dense scar

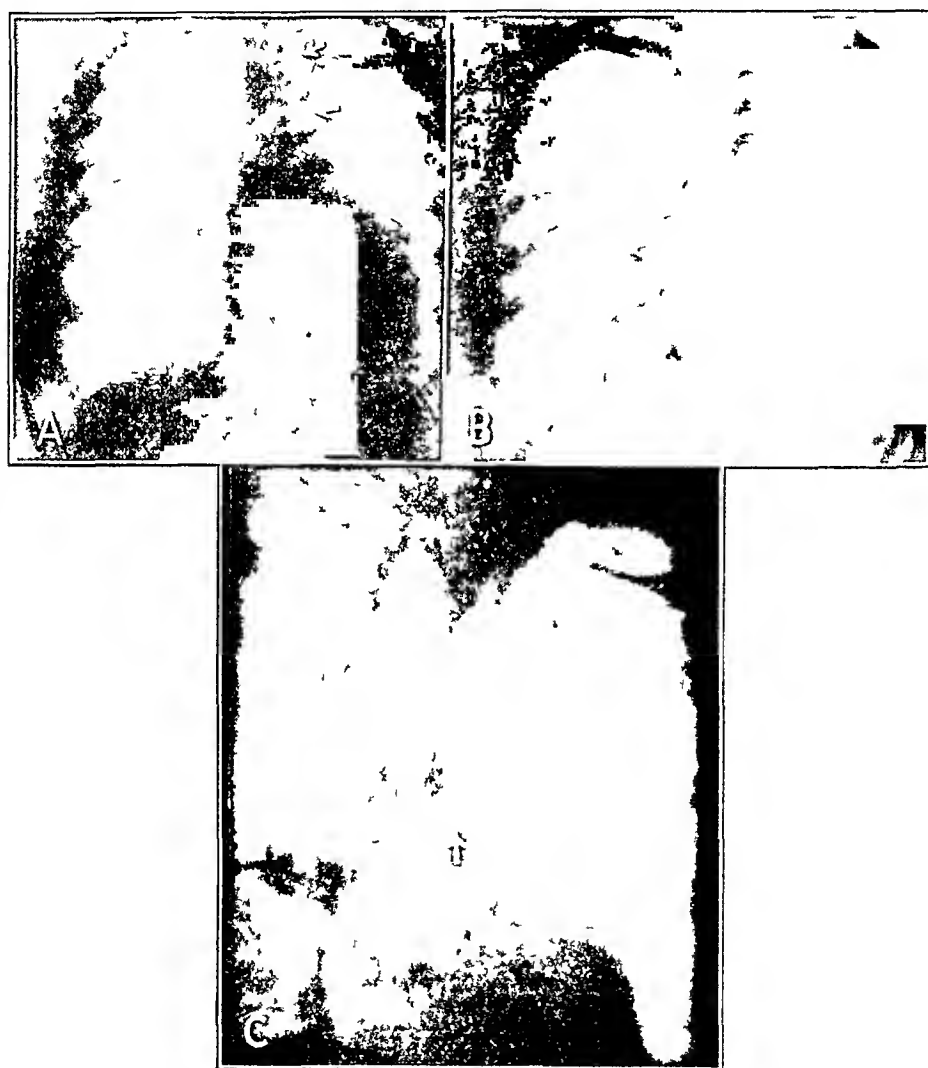


Fig 2 (case 4) —*A*, roentgenogram taken in June 1935. Despite pneumothorax, the trachea (arrows) and the heart are pulled to the left. *B*, roentgenogram taken in January 1937, after discontinuation of pneumothorax, showing atelectasis of the left lung. *C*, bronchogram showing the left main bronchus reduced to a small slit.

tissue. Bronchographic study (fig 2 *C*) showed the left main bronchus reduced to a small slit, ending in a blind pouch  $\frac{1}{2}$  inch (12 cm) from the bifurcation. During the patient's stay in the hospital the sputum became free of tubercle bacilli. The left pleural space was gradually obliterated, with retraction of the heart and

trachea far to the left and narrowing of the intercostal spaces on that side (fig 2 B) When last seen, in March 1938, the patient still suffered from severe attacks of dyspnea and wheezing, she had a new lesion in the right lung, and smears of the sputum again showed tubercle bacilli

CASE 5—I K, a woman aged 28, was found to have a tuberculous lesion of the upper lobe of the right lung in February 1935 Artificial pneumothorax resulted in symptomatic improvement for ten months, after which cough reappeared and she noted wheezing from the center of the chest, she expectorated a number of "bronchial casts" Smears of the sputum revealed tubercle bacilli Bronchoscopic study at another hospital showed the right main bronchus to be constricted by a mass of rough, friable tissue, there was an ulceration of the bronchial wall, which extended up into the trachea, and purulent material was obtained from beyond the constriction The patient was then followed in the outpatient department of the Lenox Hill Hospital for a year, during which time the sputum contained no tubercle bacilli Dyspnea and wheezing would reappear, and a refill would give relief Every two weeks the stricture was dilated and a solution of silver nitrate was applied to the ulcer The last bronchoscopic examination, in October 1937, showed the lumen of the right main bronchus to be reduced to about  $\frac{1}{8}$  inch (0.32 cm) in diameter by a circular smooth scar Smears of the sputum began to show tubercle bacilli about this time, and the patient was admitted to the Montefiore Hospital in November

Examination showed pneumothorax on the right with about 60 per cent collapse of all lobes, the heart and trachea were drawn to the right Numerous smears of the sputum failed to disclose tubercle bacilli The intrapleural pressure was very low The patient would not give permission for bronchoscopic and bronchographic examinations and was discharged soon afterward in relatively good condition In May 1938 her general condition was unchanged

CASE 6—B M, a woman aged 27, had tuberculosis of the left lung in April 1935 Pneumothorax was induced at the New York State Hospital at Ray Brook, N Y The sputum, however, persistently showed tubercle bacilli in smears Persistent bronchial rales were heard over the upper lobe of the left lung, which caused a bronchial lesion to be suspected The patient was transferred to the Montefiore Hospital in October 1936

She had never noted wheezing Examination showed pneumothorax on the left, the collapsed lung shadow was rather dense and homogeneous, and the trachea and heart were in the midline The sputum contained tubercle bacilli In the next few months a large amount of fluid appeared in the left pleural cavity, this fluid was always clear and sterile Bronchoscopic study in March 1937 showed the lumen of the left main bronchus at the level of the orifice of the branch to the upper lobe to be narrowed to about one-half its normal diameter The lateral wall was ulcerated and covered with a whitish exudate, and the bronchus to the upper lobe was narrowed by a similar ulcerostenotic process Biopsy showed tuberculous granulation tissue

In the course of the next two months the fluid gradually absorbed The heart and trachea were drawn far to the left The patient returned to the care of her private physician, who in March 1938 reported that there had been little change There was occasional wheezing from the left side of the chest, and rhonchi could be heard on this side She declined to reenter the hospital for further treatment

CASE 7—R F, a woman aged 33, first had pulmonary symptoms in 1934. On her admission to the country sanatorium of the Montefiore Hospital in April 1935, examination showed a minimal lesion of the upper lobe of the right lung. Smears of the sputum revealed tubercle bacilli. A small triangular shadow was seen in the right paratracheal region (fig 3 *A*). The shadow became larger and denser until, in September, it assumed definitely the appearance of an atelectatic lobe (fig 3 *B*). The patient refused to permit bronchoscopic study. Pneumothorax was induced, but collapse was hindered by several adhesions. Refills were given at intervals during the next two years, but the state of the patient's health was only fair, and tubercle bacilli were alternately present and absent in smears of the sputum.

The patient was admitted to the Montefiore Hospital in September 1937. She had never detected a wheeze, nor were rhonchi heard. A roentgenogram showed partial pneumothorax on the right. The trachea and heart were in the midline but were drawn somewhat to the right on inspiration. Bronchoscopic study showed



Fig 3 (case 7)—*A*, roentgenogram taken April 30, 1935. Note the small shadow in the right paratracheal region. *B*, roentgenogram taken on September 14. The shadow has become larger, indicating atelectasis of the upper lobe of the right lung.

the main bronchus of the right lung to be almost completely obstructed just below the bifurcation of the trachea by a smooth area of stenosis with an apparently intact mucosal surface, below this area of stenosis there was visible for a short distance a ragged bronchial wall which narrowed the lumen and was covered with slough and thick secretion. Biopsy showed tuberculous granulation tissue. The patient requested discharge from the hospital and when last heard from was in Colorado.

CASE 8—E W, a woman aged 29, had pulmonary tuberculosis in 1931. A roentgenogram taken in 1933 showed a triangular shadow in the right parasternal region, the trachea and heart were in the midline. She was admitted to the hospital in December 1934. Dyspnea was marked. Physical signs were not remarkable. The parasternal shadow was still present (fig 4 *A*). The sputum contained tubercle bacilli. Pneumothorax was induced in February 1935. In July the patient complained of a "raw sensation in the bronchi," and an expiratory stridor to the right of the sternum was detected. The intrapleural pressure at this time

was somewhat low. She had high fever and appeared acutely ill. In the latter part of 1935 a dense shadow appeared in the upper portion of the right lung field, gradually progressing over the entire side. Pneumothorax was discontinued, whereupon the heart and trachea shifted markedly to the right (fig 4B). Bronchoscopic study in March 1936 showed the right main bronchus to be narrowed from its orifice downward by protrusion inward of the lateral wall, which was covered with exudate. The patient's condition became progressively worse. Dyspnea and wheezing were intense. The left lung became involved. Death occurred in August 1936.

Autopsy showed the right lung to be reduced to a mass 10 cm in diameter, which did not contain air but did contain a few irregular cavities. The mucosa of the right main bronchus was reddened, thickened and piled up in corrugated fashion, several areas appeared ulcerated. Microscopic examination showed the bronchial wall to be extremely thickened by dense hyalinized fibrous tissue. Tubercles were seen in the submucosa.

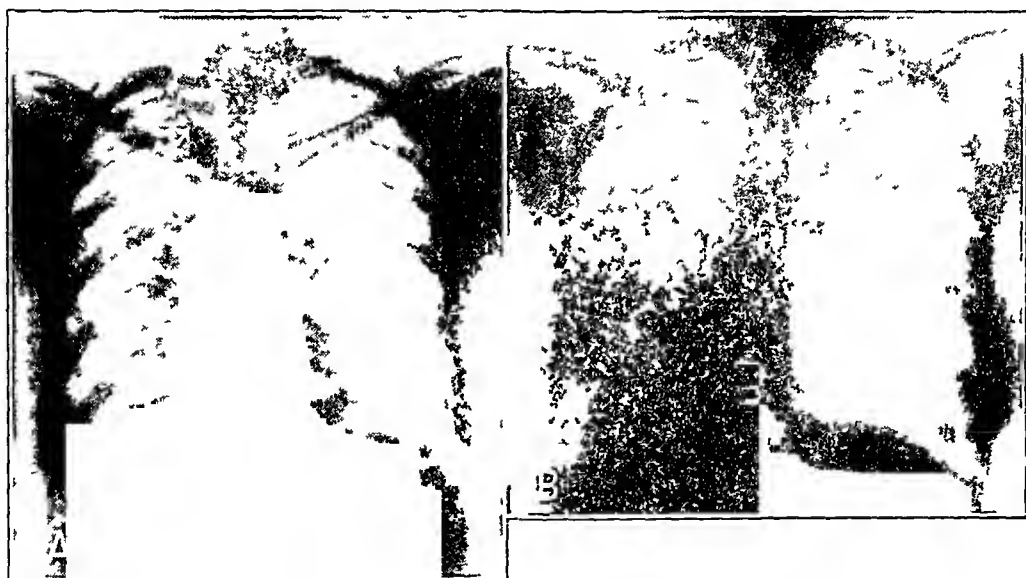


Fig 4 (case 8)—A, roentgenogram taken in December 1934. Note the triangular paratracheal shadow. B, roentgenogram taken in February 1936. There is atelectasis of the right lung.

CASE 9—J. P., a woman aged 30, was admitted to the Montefiore Hospital in August 1935 with pulmonary tuberculosis of at least three and one-half years' duration. A roentgenogram showed a shadow in the right paratracheal region suggestive of atelectasis of the upper lobe. The heart was pulled slightly to the right. Bronchoscopic study showed the orifice of the bronchus to the upper lobe of the right lung to be represented by a dimple. A bronchogram showed a small blind pouch protruding from the right main bronchus at the level of its bifurcation, the apical branch of the lower lobe bronchus supplied the area normally in the position of the upper lobe.

There were several exacerbations and remissions of the disease. The paratracheal shadow persisted. In 1936 a cavity appeared in the upper part of the right lung field. Pneumothorax was induced. During this period the patient detected wheezing over the right side of the chest, a loud rhonchus was heard in the right parasternal area. After section of the adhesions the sputum became

free of tubercle bacilli. The collapsed upper lobe was pictured in the roentgenogram as a small dense triangular shadow, the heart and trachea were drawn slightly to the right. At the time of writing pneumothorax treatment is being carried out in the outpatient department, and the patient is feeling well.

CASE 10—R M, a woman aged 20, entered the country sanatorium of the Montefiore Hospital in December 1935. At this time a roentgenogram showed mottling throughout the right lung. Pneumothorax was induced, good collapse was obtained and the sputum soon became free of tubercle bacilli. About six months later (October 1936) it again showed tubercle bacilli, and at about this time the patient noted a wheeze coming from the right side of the chest. Pneumothorax was maintained. During the first five months of 1937 the collapsed upper lobe gradually began to shrink, so that by May it appeared roentgenographically as a dense triangular shadow (fig 5A), the trachea and heart were only slightly pulled to the right. Bronchoscopic examination in November 1937 showed the bronchus to the upper lobe of the right lung to be pushed downward, the lumen was narrowed, and the mucosa was congested and bled easily. A specimen taken for



Fig 5 (case 10) —A, roentgenogram taken in May 1937, during the course of pneumothorax treatment. The dense triangular shadow represents the atelectatic upper lobe of the right lung. B, roentgenogram taken in March 1938, after discontinuation of pneumothorax treatment. Collapse of the upper lobe of the right lung has persisted. The heart and the trachea are drawn to the right, suggesting beginning obstruction of the main bronchus.

biopsy showed tuberculous granulation tissue. Pneumothorax was discontinued in January 1938. The patient's condition remained good. The sputum was mostly free of tubercle bacilli, but occasionally a smear showed these organisms. Wheezing became less frequent. After discontinuation of the pneumothorax the lower and the middle lobe of the right lung gradually expanded, pushing the atelectatic upper lobe upward (fig 5B). The heart and trachea were drawn further into the right side of the chest, and the interspaces became very narrow, we suspected from this that occlusion of the main bronchus was occurring. In May there was sudden severe hemoptysis, followed by spread of the disease to the lower lobe of the right lung and a constitutional reaction. The sputum began constantly to yield tubercle bacilli.

CASE 11—I S, a woman aged 62, was admitted to the Montefiore Hospital with pulmonary symptoms of three years' duration. She was emaciated. The left

side of the chest was flat. There was dullness over the entire upper lobe of the left lung, with distant bronchial breathing and numerous rales. A roentgenogram showed a dense shadow, sharply demarcated, occupying the site of the upper lobe. Bronchoscopic study showed the left main bronchus to be narrowed by moderately soft fibrous tissue, a slit remained, which could be dilated to 4 mm. A bronchogram showed the bronchus to be narrowed, apparently by pressure from without.

The course was progressive. Extensive bilateral cavitation occurred, and the patient died seventeen months after her admission to the hospital. Autopsy showed the left lung to be one-half the size of the right. The upper lobe was airless and contained several cavities. The lower lobe was emphysematous, nodular and fibrotic. The left main bronchus was reduced to a slit. A large, partly calcified lymph node in the infratracheal region seemed to compress the bronchus. The peripheral bronchi were dilated. Microscopic study of the bronchial wall showed large amounts of hyalinized fibrous tissue around the cartilages. Tubercles were seen in the submucosa. No epithelium could be observed.

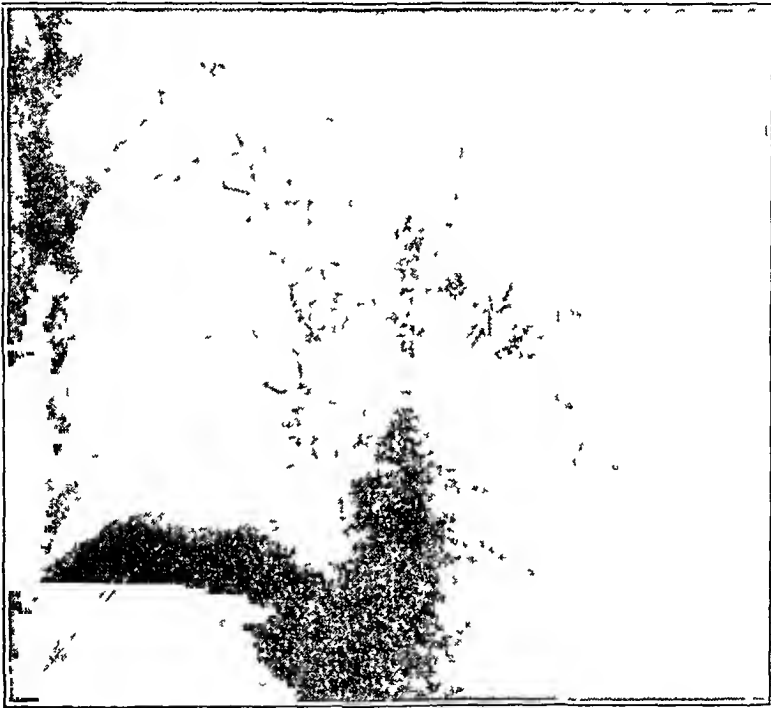


Fig 6 (case 12) —Bronchogram showing a stricture of the left main bronchus

CASE 12—R K, a woman aged 37, was found to have tuberculosis of the left lung in 1935. Pneumothorax was induced elsewhere and she was admitted to the Montefiore Hospital in September. Examination showed hydropneumothorax on the left, the heart and trachea were pushed to the right. The fluid became purulent, and pneumothorax was discontinued. The pleural cavity gradually obliterated itself, and early in 1937 the mediastinum began to shift to the left. In March the patient detected wheezing from the left side of the chest, and an inspiratory rhonchus was heard over the left paravertebral region. The left lung field became dense. Bronchoscopic examination in November showed the left main bronchus to be occluded 15 cm below the bifurcation by a firm, fibrous stricture, a lumen about 3 mm in diameter being left. Bronchographic examination showed a partial stricture of the bronchus (fig 6).

CASE 13—B P, a woman aged 22, was found to have tuberculosis of the upper lobe of the right lung in 1934. Pneumothorax was attempted and abandoned. In 1936 she detected a wheeze arising from beneath the sternum, this appeared intermittently. She was admitted to the Montefiore Hospital in August 1937. On examination a rhonchus was heard over the right paravertebral region. In the ensuing three months the right lung field became dense, the interspaces became narrow, and the heart and trachea moved into the right side of the chest (fig 7). Bronchoscopic examination revealed the carina to be thickened, with resultant

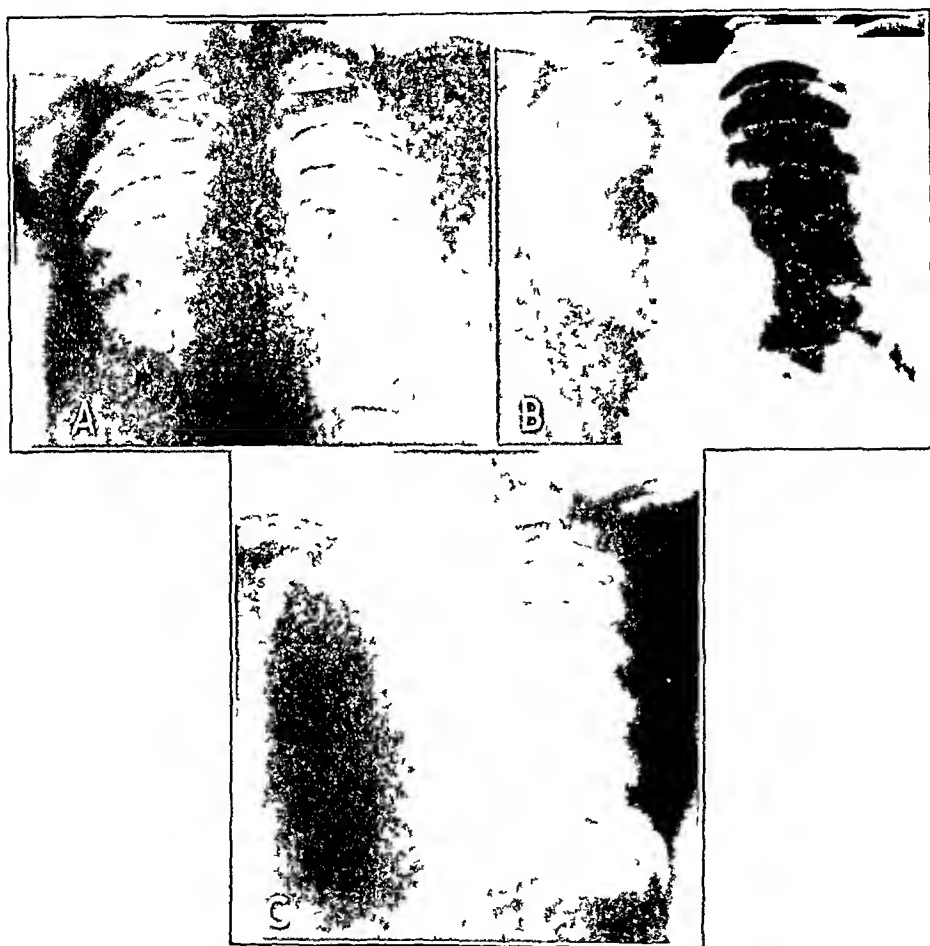


Fig 7 (case 13)—*A*, roentgenogram taken in July 1937. No evidence of atelectasis is present. *B*, roentgenogram taken one month later. The mediastinum is beginning to shift to the right. *C*, roentgenogram taken four months later. There is further progression of the atelectasis.

narrowing of the orifice of the left main bronchus. The right main bronchus was completely occluded by swelling of the mucosa and obstruction of the residual lumen by slough and pus; on removal of this secretion the lumen was about 5 mm in diameter, and extensive ulceration of the wall was seen. Bronchographic study showed the right main bronchus to be reduced to about one quarter of the normal caliber. The bronchus to the upper lobe was somewhat narrowed and

communicated with a large series of cavities. All that could be seen of the middle and lower lobe bronchi was a stem bronchus about  $\frac{3}{4}$  inch (1.9 cm) long, ending in a few ectatic sacculations.

CASE 14—B. G., a woman aged 30, was admitted to the Montefiore Hospital in August 1934 with a three year history of pulmonary symptoms marked by hemoptysis on numerous occasions. Physical examination showed dulness over the entire left lung. Smears of the sputum disclosed tubercle bacilli. A roentgenogram showed a dense homogeneous shadow over the entire left lung, a large cavity with a fluid level apparently within lung tissue was noted in the upper portion of the lower lobe of the left lung, the trachea and heart were retracted to the left. Pneumothorax was induced, but numerous adhesions prevented satisfactory collapse.

The patient's condition remained unchanged, but the sputum gradually became free of tubercle bacilli. In 1937 an inspiratory and expiratory rhonchus was heard over the left side of the chest. Bronchoscopic study showed a stricture of the left main bronchus above the orifice of the bronchus to the upper lobe, the lumen was narrowed to about 3 mm, the mucosa seemed intact, there was also kinking of the main bronchus below the stricture, so that practically no aeration of the lung was obtained unless the bronchus was straightened.

CASE 15—B. G., a woman aged 40, had pulmonary tuberculosis in 1910 and had spent five years in several hospitals, after which the disease was considered arrested. Exacerbation of the symptoms led to her admission to the Montefiore Hospital in July 1934. Examination showed retraction of the entire left side of the chest, there were flatness and distant breath sounds over the left lung. A roentgenogram showed a dense shadow over the left lung field, the interspaces were narrowed, the heart and trachea were drawn to the left. Bronchoscopic study showed the left main bronchus to be narrowed to a diameter of 2 mm about 2 cm below the carina. The mucosa was red and granular. Bronchographic study (fig. 8) showed the main bronchus to end in a blind pouch 2.5 cm below the bifurcation. Aspiration of the left pleural cavity yielded thick pus, a bronchopleural fistula was demonstrated. Symptoms of mental disease subsequently developed, and the patient was discharged to a psychiatric institution.

CASE 16—J. P., a woman aged 64, had hoarseness and cough four years prior to her admission to the hospital. Nine months previously she was treated for "pneumonia" of the upper lobe of the right lung and was in bed six weeks. Cough and expectoration persisted, and she was admitted to the Montefiore Hospital in December 1937.

She stated that she had had "asthma" twelve years before but that it had gradually disappeared. She had noted its return during the previous year. On physical examination she was dyspneic on the slightest exertion. A wheeze could be heard at some distance, thus she localized to the right side of the chest. There were dulness and distant breath sounds over the middle lobe of the right lung, where a loud inspiratory rhonchus was heard. Roentgen examination (fig. 9) showed a triangular shadow corresponding to an atelectatic middle lobe, there was no shift of the mediastinum. Repeated examinations of the sputum failed to reveal tubercle bacilli.

Bronchoscopic study showed creamy pus coming from the upper lobe of the right lung. On the mesial wall of the right main bronchus, opposite the orifice of the branch to the lower lobe, a thickened, healed ulceration was seen, in the



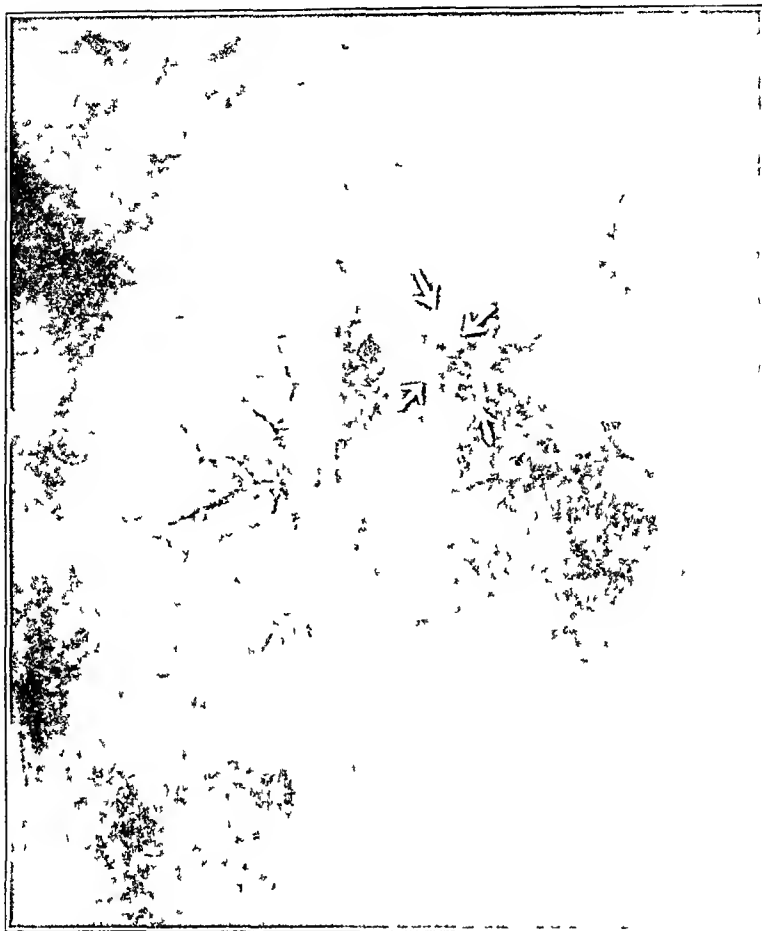


Fig 8 (case 15) —Bronchogram showing the left main bronchus ending in a blind pouch

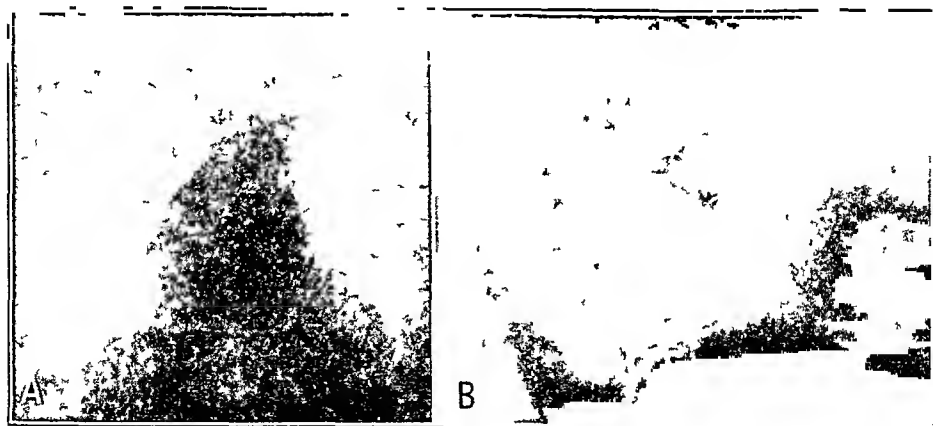


Fig 9 (case 16) —*A*, atelectasis of the middle lobe of the right lung *B*, lateral view

midst of which there was an area of anthracotic pigmentation 6 mm in diameter. Below this the bronchus was narrowed so that the instrument could not be passed, the bronchus to the middle lobe appeared completely occluded by scar tissue. After bronchoscopic examination the patient became dyspneic and required oxygen therapy. Physical and roentgen examination indicated atelectasis of the lower lobe of the right lung. The symptoms and signs cleared, and in the course of a week the original picture was restored. Bronchographic study showed a small anterior radicle of the right main bronchus, which lay in the position normally occupied by the bronchus to the middle lobe of the lung, there a small collection of iodized poppyseed oil was seen, and the bronchus terminated  $\frac{1}{4}$  inch (0.64 cm) from its point of origin.

CASE 17—B F, a woman aged 59, was admitted to the Beth Israel Hospital in April 1936, complaining of fever, cough and pain in the right chest of two weeks' duration. On the day of admission she had noted some blood-streaked sputum. She had suffered from "bronchial asthma" for eighteen years and was supposed to be sensitive to feathers. On examination she appeared acutely ill. The temperature was 104 F. The respirations were rapid and shallow. She was moderately cyanosed. There were dullness and suppressed breath sounds over the lower part of the right lung. Numerous musical rales were heard throughout both lungs. The sputum did not contain tubercle bacilli. The temperature fell to about 100 F in a few days. Roentgenograms showed complete lack of aeration of the lower and the middle lobe of the right lung, the trachea and heart were in the midline. Bronchoscopic study on April 24 showed the carina to be somewhat thickened, at a level just below the orifice of the bronchus to the upper lobe the medial and anterior walls of the main bronchus showed thickened mucosa, forming an area of stenosis. There were several anthracotic-appearing areas studding it. Biopsy failed to reveal tumor or tuberculous tissue. It was nevertheless felt that the patient was suffering from a neoplasm. She was given high voltage roentgen therapy. Little improvement was noted, and she was discharged twelve weeks after admission.

After her discharge from the hospital, the cough persisted. Otherwise she felt well. No wheezing was noted. She was readmitted for further study in December 1937. Examination showed atelectasis of the middle and the lower lobe of the right lung, there was deviation of the trachea to the right and slight elevation of the right half of the diaphragm. The sputum was sterile. Bronchoscopic study on December 21 showed the bronchus to the upper lobe of the right lung to be narrowed to one-half its normal caliber, at a point 0.5 cm below the orifice of this bronchus the main bronchus was stenosed in a funnel arrangement, with a reduction in caliber to about 3 mm, at this point numerous anthracotic spots studded the mucous membrane. A specimen taken for biopsy revealed no significant lesion.

CASE 18—G H, a man aged 70, had cough and hemoptysis in 1931. Roentgen examination at another hospital showed a dense, irregular shadow in the mid-portion of the lung, the intercostal spaces were narrowed, and the heart was drawn to the right. It was felt that the patient was suffering from bronchogenic carcinoma, and intensive roentgen therapy was given. He continued to suffer from cough, hemoptysis, pain in the right side of the chest and loss of weight and was admitted to the Montefiore Hospital in December 1934. Physical and roentgen findings indicated atelectasis of the entire right lung, with marked shrinkage of the hemithorax. A roentgenogram showed several calcified areas in the

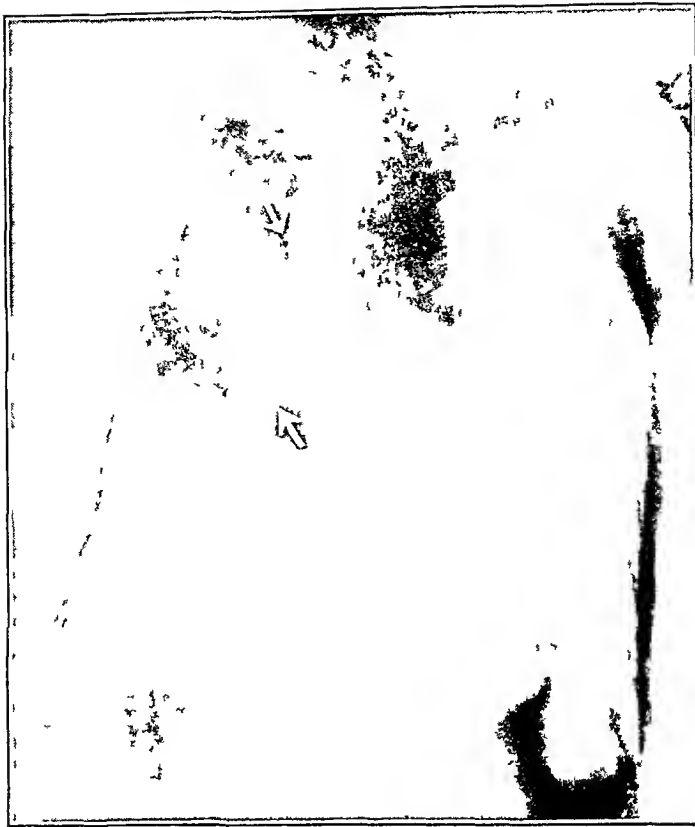


Fig 10 (case 18) —Shrinkage of the entire right side of the chest, due to atelectasis. The arrows point to calcified areas in the hilus of the right lung, representing lymph nodes. The upper of these is probably in the main bronchus.



Fig 11 (case 18) —Postmortem specimen. The posterior view of the heart and the right lung is shown. Note the calcified lymph node breaking into the main bronchus.

right hilar region (fig 10) Smears of the sputum did not reveal tubercle bacilli. Bronchoscopic study showed the right main bronchus to be almost completely occluded, the impression was that a foreign body was present. It was planned to repeat the bronchoscopic examination, but the poor condition of the patient prevented it, and he died three weeks later.

Autopsy showed the left lung to be voluminous. The right lung was shrunken and airless. The right main bronchus just behind the bifurcation contained a hard body encrusted with calcium salts, which eroded and perforated the bronchial wall (fig 11). This obviously was a lymph node which had perforated into and occluded the bronchus.

CASE 19—M W, a man aged 26, consulted one of us (H W) in December 1930. Nine years previously he began to have hemoptysis. A diagnosis of pulmonary tuberculosis was made, and the patient had since been treated in various institutions. Examination showed involvement of the apex of the left lung. A roentgenogram showed displacement of the trachea to the left, the bronchus of the upper lobe of the left lung was deformed, narrowed and displaced downward by a mass just outside it, which resembled a large lymph node. Bronchoscopic study revealed a superficial ulceration on the floor of the left main bronchus near the orifice of the branch to the upper lobe of the lung. Phrenicotomy resulted in temporary improvement, but when the patient was seen in March 1936, there was progression of the lesion in the apex of the left lung. He continued to have mild hemoptysis from time to time.

CASE 20—H C, a man aged 44, was first admitted to the country sanatorium of the Montefiore Hospital in February 1928. Physical signs were not remarkable. The sputum yielded bacteria on culture. A roentgenogram showed a large round cavity in the apex of the left lung (fig 12 A). The patient was discharged and was admitted subsequently a number of times, without any significant change in his condition. When he was admitted to the hospital in February 1934, however, it was found that the site of the cavity in the apex of the left lung was occupied by a dense homogeneous shadow, a new, larger cavity was present below it (fig 12 B). This picture was interpreted as indicating blockage of the tributary bronchus. Bronchoscopic examination on Sept 17, 1935, showed the bronchus to the upper lobe of the left lung to be narrowed, the lumen of its paravertebral branch was reduced to a slit. Bronchographic study showed the apical branches of that bronchus to be occluded just below the obliterated cavity (fig 12 C).

#### COMMENT

A study of the cases presented indicates knowledge has progressed so that bronchial tuberculosis can be clinically diagnosed. It is well to bear in mind, however, certain circumstances which stand in the way of early diagnosis. The mere presence of ulcerations or of stenosis of the bronchi does not mean that there will be characteristic or even suggestive symptoms of this condition. The bronchi in the presence of a long-standing pulmonary disease like tuberculosis may be insensitive to inflammatory changes of the mucous membranes. It is also known

from experience with tumors of the bronchi that gross organic lesions may be symptomless for long periods. One cannot avoid the conclusion that tuberculous bronchial lesions may be latent for a considerable time when one observes through the bronchoscope the occlusion of a bronchus in a patient in whom this condition had not been suspected. Furthermore, in most cases there is little or nothing in the character of the

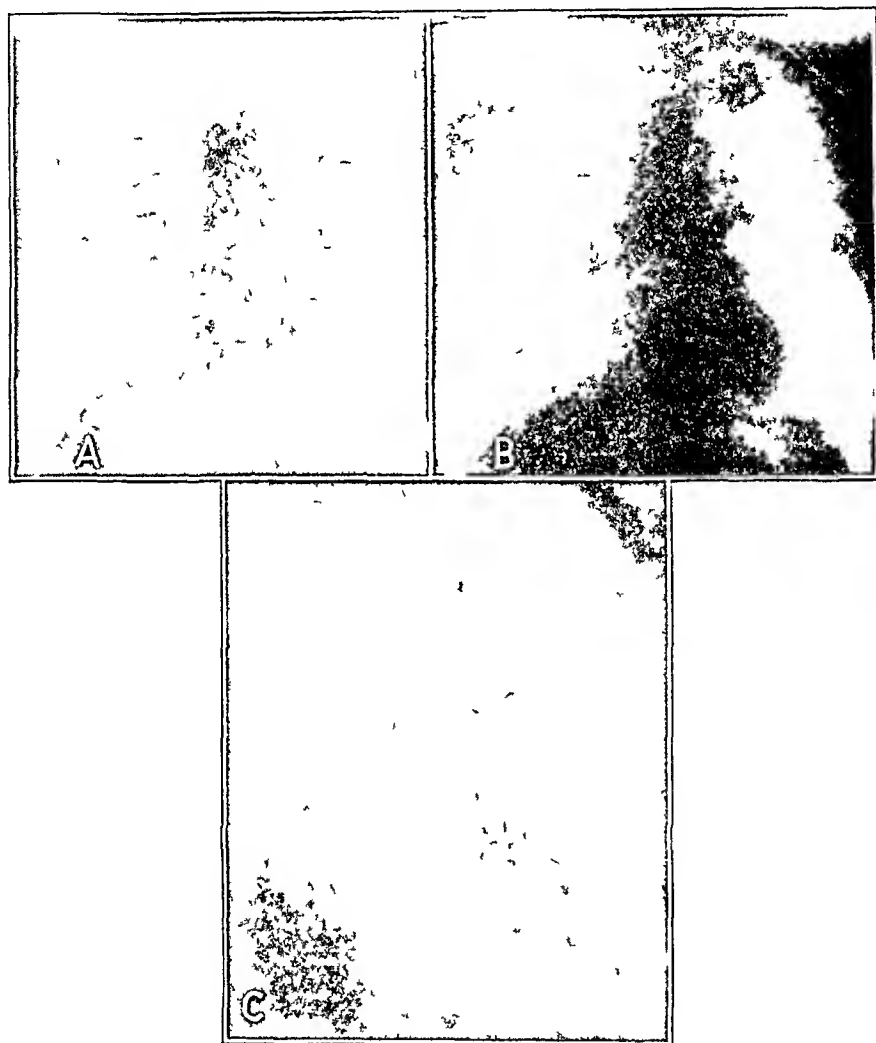


Fig 12 (case 20) —*A*, roentgenogram taken in February 1932. Note the large cavity in the upper lobe of the left lung. *B*, roentgenogram taken in May 1934. Note the cavity filled with radiopaque substance. *C*, bronchogram showing the apical branches occluded below the obliterated cavity.

cough or the expectoration which permits one to say that a bronchial factor has been added to the pulmonary disease already present.

Case 1 represents perhaps the simplest combination of symptoms which may arouse a suspicion of bronchial tuberculosis. The patient

had no cough or expectoration, and an effective therapeutic collapse of the lung left him with sputum which contained tubercle bacilli. Under these circumstances experience would warrant one to expect the sputum to be free from tubercle bacilli. Obviously the cause of this condition had to be sought elsewhere than in an open cavity, of which there was no evidence. On bronchoscopic examination a tuberculous ulcer of a main bronchus was found, from which tubercle bacilli were freely discharged. A similar explanation will apply to cases in which thoracoplasty is done and in which examination of the sputum continues to show tubercle bacilli in spite of the fact that the cavity has been adequately collapsed. This is well illustrated in case 2.

The only symptoms which may be regarded as characteristic of bronchial tuberculosis are those which result from a decrease in the caliber of the trachea or of a large bronchus. Such structural changes, impeding the passage of air into the lungs, are manifested by symptoms which have positive diagnostic value. The cases here reported illustrate most of these, which may be both subjective and objective. As they are the result of the same mechanical changes, they complement each other, so that taken together they are in many cases pathognomonic.

Among the subjective symptoms there is one which occurs with such frequency that it may be considered characteristic, namely, a wheezing sound which is usually noted by the patient as well as by the examiner. It is surprising how long a patient may have been aware of this sign without attributing any significance to it or calling it to the attention of the physician. This wheeze or rhonchus is usually low pitched and sonorous and in its most significant form is constantly present owing to a fibrous stricture of a large bronchus. However, it may appear only when granulations or mucus are lodged in a narrowed bronchus. For this reason even an inconstant sonorous rhonchus may have significance if it is always heard over the same point on the wall of the chest. When it is sufficiently loud it is heard all over the chest, although its maximum intensity is usually over the affected bronchus, and it is often so localized by the patient. When the caliber of the bronchus is contracted beyond a certain point there is a progressive decrease in the intensity of the rhonchus, until it finally disappears.

As obstructive lesions are commonly found in the main or lobar bronchi, the objective symptoms of this condition arise from the collapse of a whole lung or one of its lobes, with resulting alteration of the normal pressure relations in the chest. These changes are clearly shown

in patients in whom the lung has already been collapsed by therapeutic pneumothorax. Whenever during the course of such treatment a lobe of the lung exhibits extreme collapse without any tendency to reexpand when pneumothorax is suspended (case 10) it is proper to suspect that there may be an obstruction of the bronchus. This suspicion will find support when, in addition, a rhonchus is audible.

In this series of cases the lesion occurred most commonly in a main bronchus. In only 9 was the obstruction so complete as to result in the collapse of a whole lung. In a tenth case of obstruction of the main bronchus there was atelectasis of a single lobe (case 11). In all the other cases of lobar atelectasis, of which there were 5, the main bronchi were free of disease, the obstructive lesion involving only the lobar bronchus, which was always in the upper lobe. It is important to note that the collapse of a single lobe cannot readily be determined without roentgen examination, because it is not followed by noticeable displacement of the mediastinum. In some cases (7 and 8) the progress of a lesion from a lobar to a main bronchus could be observed by its effect on the aeration of an increasing part of the lung and by a marked shift of the mediastinum. When pneumothorax was maintained this transition was marked by a fall in intrapleural pressure.

Naturally, the respiratory function will at times be profoundly disturbed under these conditions, although the mechanism of this change is not always clear. Attacks of dyspnea similar to asthma may occur, which obviously cannot be due to closure of a single bronchus. In analysis of the cause of dyspnea in such cases other factors, such as extensive tuberculous disease of the opposite lung, must be considered. The closure of a main bronchus under these conditions would reduce the respiratory area of the whole lung field to a critical level. It will also be found in some cases that the respiratory difficulty is aggravated by the mediastinal displacement which follows massive collapse of a whole lung. In such a case (case 5) it was possible to reestablish almost normal breathing by giving refills under moderate pressure, which restored the mediastinum to its median position. In 1 instance (case 4) the patient suffered attacks of air hunger bordering on asphyxia when she assumed certain postures. This could be explained by a marked narrowing of the lower portion of the trachea, which, added to a complete stricture of one of the main bronchi, compromised the air passage to an extreme degree.

The influence of tuberculous disease of the lymph nodes on the adjacent bronchus merits some consideration. It is true that, especially

in adults, the symptoms and pathologic changes due to intrinsic tuberculous disease of the bronchi do not commonly result from the presence of enlarged tuberculous lymph nodes. However, there is ample evidence that such nodes may compress and erode neighboring structures with serious consequences to the bronchi, the pulmonary blood vessels and the lungs.

In young children the rupture of caseous lymph nodes into a bronchus has long been recognized, it occupies an important place in the pathogenesis of acute tuberculous pneumonia. The clinical symptoms due to pressure of large lymph nodes, especially in the paratracheal region, have been described by various authors (Sluka,<sup>27</sup> Rach<sup>28</sup>), who have drawn attention to the inspiratory stridor which results from pressure on the lower end of the trachea. Atelectasis of various lobes of the lung has resulted from such pressure, the effects of which may be permanent. It has even been suggested that so-called epituberculous infiltration in young children is not actually infiltration of the lung by disease but is a condition due to atelectasis of portions of the lung caused by the pressure of enlarged tuberculous lymph nodes at the hilus (Rossle,<sup>29</sup> Brock and others<sup>30</sup>).

In adults it appears that the rigidity of the larger bronchi is usually an obstacle to complete occlusion of a main bronchus by pressure of tuberculous nodes. With increasing age, also, the lymph nodes become anthracotic and indurated and contain less caseous material, so that the tendency to ulcerate into the larger bronchi is not so great. For this reason tuberculous bronchopneumonia due to this cause is undoubtedly much less frequent in adults than in children. In this series 1 patient showed gradual bronchial occlusion despite clearing of all pulmonary infiltrations. Over a period of nine years the roentgenograms showed gradual enlargement and intensification of a shadow in the hilus of the left lung, doubtless representing lymph nodes (case 3, fig 1). In another case of bronchial occlusion autopsy showed a large, partly calcified lymph node which appeared to compress the bronchus (case 11). In a third case (case 20), clinically considered one of bronchial carcinoma, a calcified lymph node was observed at autopsy which had perforated into and completely occluded the right main bronchus. We

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27 Sluka, E. Ueber Röntgenbefunde bei tuberkulösen Kindern mit expiratorischem Keuchen, *Wien klin Wchnschr* **23** 136, 1910.

28 Rach, E. Zur Klinik der Bronchialdrüsentuberkulose im Kindesalter, *Beitr z Klin d Tuberk* **32** 31, 1914.

29 Rossle, R. Die pathologisch-anatomische Grundlagen der Epituberkulose, *Virchows Arch f path Anat* **296** 1, 1935.

30 Brock, R. C., Cann, R. J., and Dickinson, J. R. Tuberculous Mediastinal Lymphadenitis in Childhood. Secondary Effects on the Lungs, *Guy's Hosp Rep* **87** 295, 1937.



have observed a number of cases not recorded here in which the bronchoscopist could demonstrate narrowing of the bronchi by pressure of large nodes without any change in the mucous membranes

The relation of tuberculous lesions of the bronchi to hemoptysis is of some clinical interest. Ulcerations and tuberculous granulations do not seem, as a rule, to give rise to severe hemoptysis. On the other hand, we have observed a number of cases in which repeated severe hemoptysis was associated with the pressure of tuberculous nodes on the major bronchi. On bronchoscopic examination the larger bronchi showed marked compression, there was congestion of the mucous membrane without any actual invasion of the bronchial walls by the tuberculous process. The nodes may at times be recognized in the roentgenogram, especially when they form clearly outlined masses in the recess between the trachea and the main bronchi. In other cases calcification of many nodes, with or without the expectoration of broncholiths, has been associated with severe hemoptysis recurring during a period of years. It is important to bear in mind that severe and fatal hemorrhage from the lungs may follow simultaneous erosion of a branch of the pulmonary artery and of the bronchial wall. This has been especially noted with older patients, in whom the only evidence of previous pulmonary disease was an anthracotic, indurated lymph node. The slow extension of the caseous center of such a node to the neighboring pulmonary artery and the bronchial wall led to rapidly fatal hemorrhage in 10 cases reported by Arnstein<sup>31</sup>. In this connection it is of interest that Vinson and Toone<sup>32</sup> recently reported a case of unexplained hemoptysis, in which they found an anthracotic lymph node protruding into the lumen. Cases 16 and 17 of this series are included in spite of the fact that neither patient showed evidence of preexisting or coexisting tuberculosis. In each case the picture was that of lobar atelectasis, and bronchoscopic study showed bronchial occlusion with anthracotic pigmentation at the site of obstruction, suggesting antecedent perforation by lymph nodes.

Recently Fleischner<sup>5</sup> and Neumann<sup>2</sup> reported further evidence of the influence of tuberculous nodes on the thoracic organs other than the bronchi. Adhesion of these nodes to the esophagus is likely to produce small traction diverticula which are easily demonstrable in the roentgenogram (fig 13). In 7 cases of this series in which the esophagus was studied with the aid of barium sulfate, diverticula were found in 2 (1 and 12). In at least 8 of our cases there is thus some evidence that hilar lymph nodes played a pathogenic role.

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31 Arnstein, A. Ueber indurierende Bronchialdrusentuberkulose als Ursache schwerer Hamoptoe bei alteren Leuten, Beitr z Klin d Tuberk 78 55, 1931

32 Vinson, P. P., and Toone, E. C. Pulmonary Symptoms Resulting from Ulceration of Hilar Nodes into a Bronchus, West Virginia M J 33 200, 1937

*Prognosis*—Since this syndrome has been recognized for only the past few years, insufficient time has elapsed for a proper evaluation of its role in prognosis. The impression to be gathered from previous reports is that patients with this complication usually do poorly. From our experience in this series, in which patients have been followed from one to four years after onset of symptoms, we agree with this impression. At the time of writing, only 1 patient is really well, and the lesion

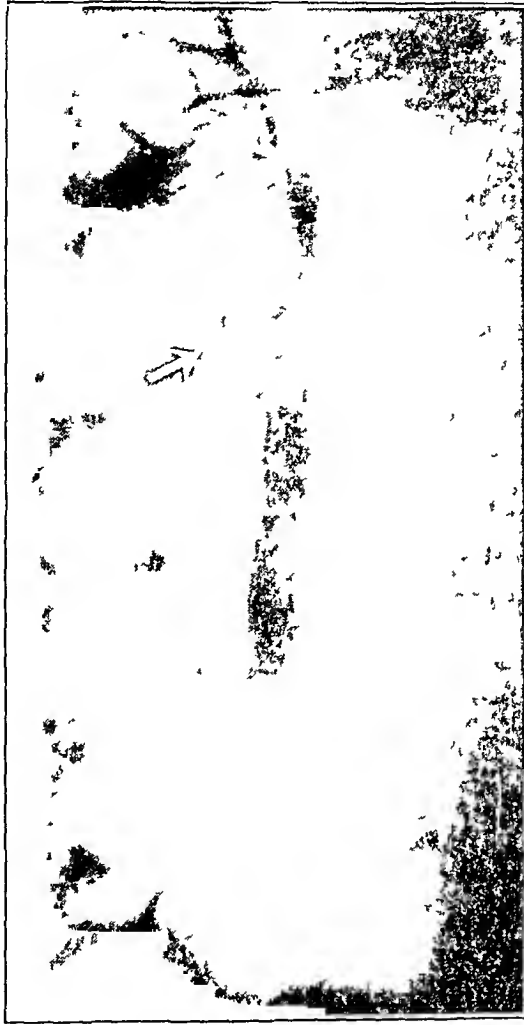


Fig 13—Esophogram showing a traction diverticulum

in his case was a simple ulcer, 3 are in good condition, the sputum containing no tubercle bacilli. All the others are suffering from active pulmonary tuberculosis, most of them being in a worse condition than when they were originally observed, and 3 have died.

There seem to be several reasons for the poor outcome. As has been previously mentioned, bronchial lesions are usually found in patients with rather far advanced pulmonary disease for whom the prognosis is poor. In more favorable cases, in which the condition is amenable to

collapse therapy, the beneficial effects of such therapy are negated by a persistent source of tuberculous sputum, with its potentialities for causing spread, located in a relatively inaccessible place and not affected by the artificial collapse. In a smaller group of cases in which the pulmonary disease has been arrested by natural or artificial means the patient may remain disabled because of the effect of stricture of the bronchus on the respiratory mechanism.

*Treatment*—It is unfortunate that tuberculous disease of the bronchi is usually a complication of advanced, more or less hopeless disease of the lungs. For this reason it is often not possible to apply any form of treatment. It is important to keep in mind what one hopes to accomplish by the treatment of a tuberculous lesion in a bronchus. It has been repeatedly shown that simple tuberculous ulcers which involve the mucous membrane respond to cauterization with such chemicals as silver nitrate (case 1). It is even likely that in many cases such ulcerations heal spontaneously. In some cases it would appear that cauterization or the removal of granulation tissue which obstructs the bronchi is desirable.

With respect to tuberculous stricture of the bronchi, which is usually due to destruction of the wall of the bronchus, including the cartilage, and replacement with fibrous tissue, it is doubtful whether any form of endobronchial treatment is indicated or is feasible. Attempts to dilate strictures of this sort are practically always unsuccessful, as the narrowing of the bronchus is progressive and cannot be affected by mechanical means. The basis of this treatment is the belief that owing to the narrowing of a bronchus drainage from distal portions of the bronchial tree and of the lung is interfered with. Whether this is true or not, it would seem from our experience with the treatment of tuberculosis by collapse that bronchial drainage is much less important in the process of cure than physiologic rest of the lung. We have in some cases observed the partial occlusion of bronchi without any evidence of aggravation of the tuberculous process because of a failure of secretions to drain through them. On the contrary, in rare cases in which nature has succeeded in completely occluding a bronchus, the influence on the pulmonary lesion, even including cavities, has seemed, for a time at least, to be salutary. Unfortunately, tuberculous lesions of the bronchi, even when they produce extreme narrowing, practically always leave a small lumen through which tubercle bacilli may gain access to the general bronchial tree and thus infect other parts of the lung. If there is any merit in a procedure which could completely exclude a tuberculous lesion from the bronchial tree by complete occlusion of the bronchus, it would seem more logical to occlude than to dilate the stricture.

Unfortunately, it has not been possible, at least in human beings, to produce such a complete closure of a bronchus by means of eschaeotic agents

#### SUMMARY AND CONCLUSIONS

By means of bronchoscopic and bronchographic study, confirmation of the diagnosis of tuberculosis of a major bronchus, clinically suspected, is possible

Such lesions are more common than has been thought

In most cases infection occurs by implantation of bacilli derived from peripheral pulmonary lesions, in a smaller number mediastinal lymph nodes may involve the bronchial wall

The lesions are similar to tuberculous lesions elsewhere in the body, as a result of healing, fibrous strictures of the bronchi may occur, such strictures are rarely complete

A simple ulceration or granuloma may be suspected when examination of the sputum continues to show tubercle bacilli after adequate collapse of cavities by natural or artificial means

A wheeze and an accompanying rhonchus, when persistent, are symptoms of bronchial obstruction

Objectively, atelectasis of a lobe or lobes is the outstanding manifestation, usually there is close correlation between the location of the involved lobe and that of the stenosed bronchus. Atelectasis of a lobe, unlike similar involvement of a whole lung, causes no appreciable mediastinal displacement. The onset of atelectasis of a lung during pneumothorax therapy is indicated by a fall (increased negativity) in intrapleural pressure

Alterations in the mechanism of respiration may result

Severe hemoptysis is occasionally the result of pressure of lymph nodes on the bronchus

Cases of bronchial obstruction with no clinical evidence of pulmonary or glandular tuberculosis are reported, in such cases obstruction is due to perforation of the bronchial wall by anthracotic lymph nodes

The general prognosis is poor, though not necessarily so

Simple ulcerations may heal spontaneously or may be amenable to cauterization

Dilation of strictures is deemed inadvisable

A method of producing complete closure of the strictured bronchus would be desirable, this has not yet been achieved

Drs R Kramer and M Som performed the bronchoscopic studies. Drs L H Siltzbach and M J Robin made the bronchograms. Drs H Neuhoef and I Kross furnished data and permitted us to report case 2. Dr B Stivelman gave us permission to reproduce figure 2A (case 4), and Dr A A Epstein allowed us to report case 17.

# OSCILLOMETRY IN DIAGNOSIS OF ARTERIO-SCLEROSIS OF THE LOWER EXTREMITIES

A NEW METHOD OF APPLICATION

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CLEVELAND

The oscillometer is an instrument which measures in arbitrary units the amount of pulsation transmitted to a pneumatic cuff applied to a segment of an extremity. An excellent discussion of the history of oscillometry and of the nature and use of the available instruments, with bibliography, has been given by Samuels.<sup>1</sup>

Oscillometry has been advocated as a simple means of detecting decreases in arterial pulsation in peripheral arteriosclerotic disease. However, practical application of the science for this purpose by my associates and me proved disappointing, because the results obtained were often confusing. There is normally considerable variation in oscillometric readings recorded at the same level of an extremity in different persons. Thus at the supramalleolar level (the region just proximal to the ankle joint, corresponding approximately to the distal fourth of the leg), readings between 1 and 10 comprise the "normal" range. We, as will be shown, have recorded readings between 1 and 4 at this level in cases of peripheral arteriosclerotic disease. The confusion engendered is obvious. Our observation indicates that of two oscillometric readings of the same magnitude taken from different persons at a given level of an extremity one may indicate a normal and the other a grossly subnormal condition.

Variations in the size and tonus of the arterial trunks of the segment being tested—variations which, in turn, are related to the physical development of the limb and to its metabolic activity, respectively—are probably responsible for the fact that there is no standard normal oscillometric reading for any given level of an extremity. (Individual variations in the magnitude of the initial change in intra-aortic pressure, propagation of which constitutes the pulse, are also important in this regard.)

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1 Samuels, S. S. *The Diagnosis and Treatment of Diseases of the Peripheral Arteries*, New York, Oxford University Press, 1936.

In figure 1 two oscillometric tracings are shown. Each was taken at the left ankle of a young woman free of vascular disease. One tracing was taken early in the morning just before she started her day's work, the other at the end of the same day after a long period of work which involved considerable walking. The second tracing shows an increase in the amplitude of the pulse and illustrates the effect of increased metabolic activity on arterial pulsation.

Figure 2 shows a tracing taken at the left ankle of a fairly muscular young man. Comparison with figure 1 illustrates the difference in amplitude of pulse between these two persons, one robust, the other slender.

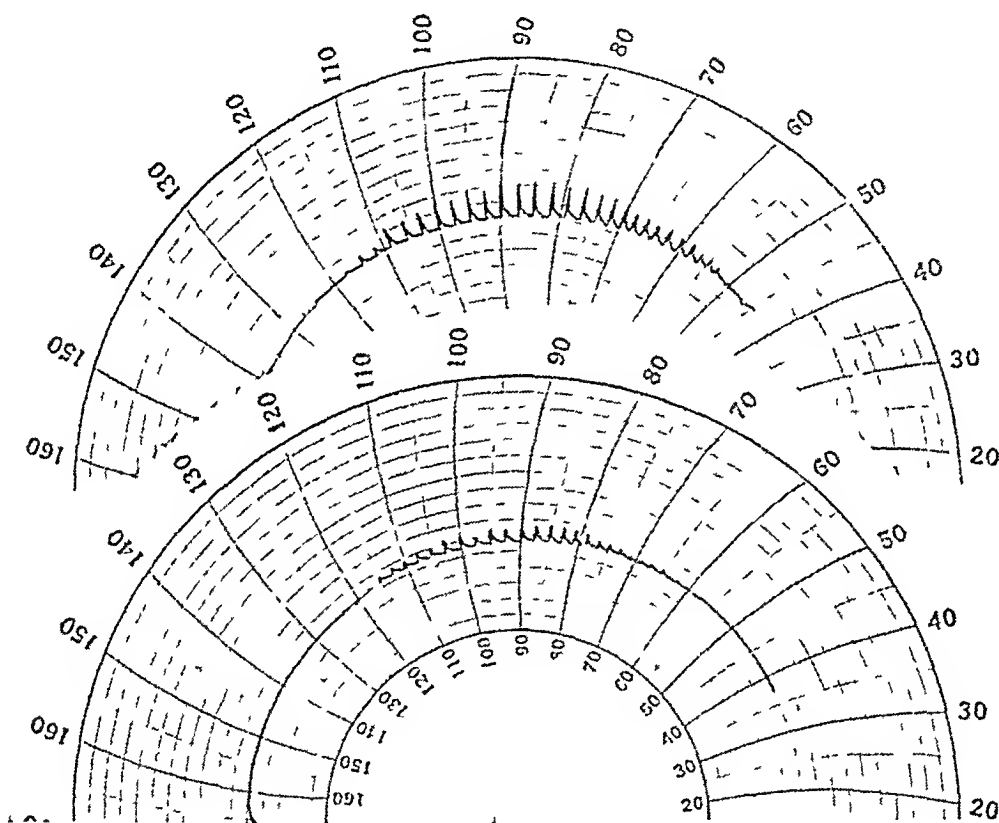


Fig 1—Oscillometric tracings taken at the left ankle of a young woman who is 22 years old, weighs 120 pounds (54.4 Kg) and is free of vascular disease. The lower tracing was taken before and the upper tracing after a period of work involving considerable walking. Note the increase in the amplitude of the pulse. (The length of the longest spike is taken as the measurement of the amplitude.)

That corresponding differences in blood pressure do not necessarily accompany differences in oscillometric readings is illustrated by figure 3. Two tracings are shown, one taken from the left wrist, the other from the midbrachial region of the left arm. Although the systolic and the diastolic pressures are almost identical, the pulsation at the brachial level is greater.

Our problem, then, was to find some simple way of determining whether an oscillometric reading, irrespective of its absolute magnitude, represented a decrease in arterial pulsation, and if so, how great a decrease

We started with the premise that since peripheral arteriosclerotic disease involves the lower extremities to a much greater extent than it

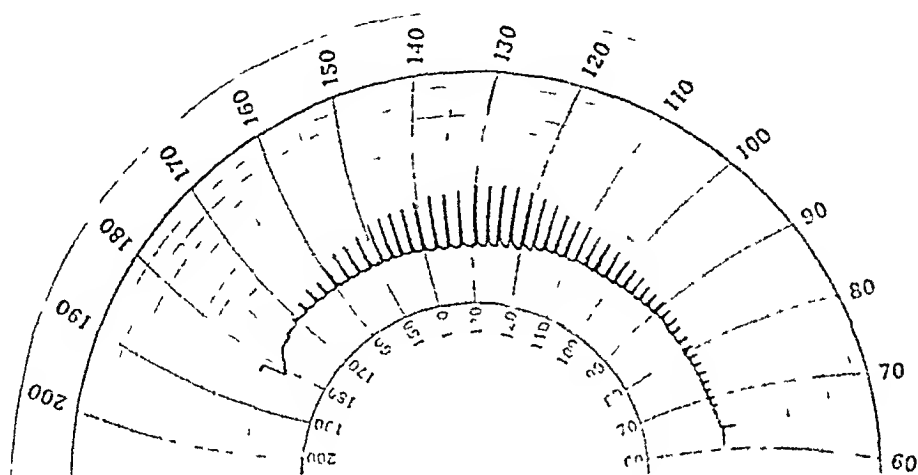


Fig 2—Oscillometric tracing taken at the left ankle of a fairly muscular young man 32 years old and weighing 167 pounds (75.7 Kg) Compare this tracing with those in figure 1, and note the difference in amplitude of pulse

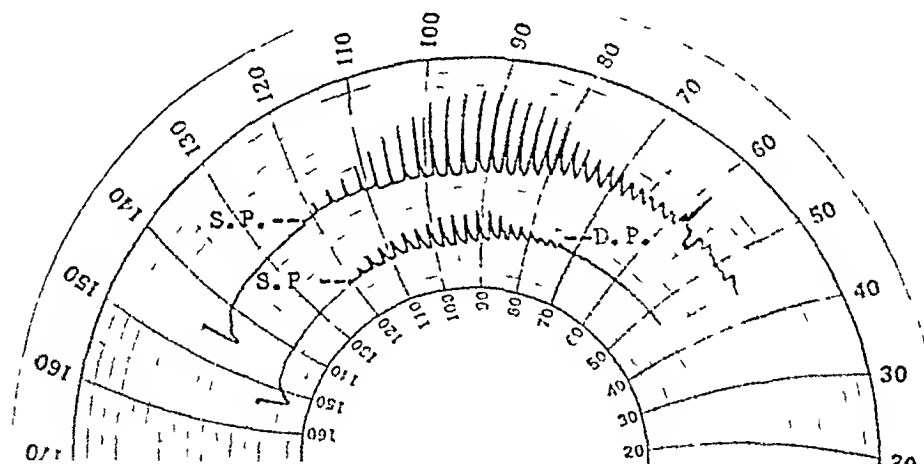


Fig 3—Oscillometric tracings illustrating the difference in amplitude of the pulse at different levels of an extremity, although the systolic (S P) and the diastolic (D P) pressures are almost identical The lower tracing was taken at the left wrist of a young man 32 years old, the upper tracing at the midbrachial region of the same arm

does the upper, oscillometric readings at any given level in the lower extremities should, as the disease progresses, decrease proportionately more than those at any given level in the upper extremities

To test this hypothesis, we first took a series of oscillometric readings at the supramalleolar level and at the distal third of the corresponding forearm in active young adults free of vascular disease to establish the ratio that exists normally between oscillometric readings at these two levels. The supramalleolar region was chosen because arteriosclerotic disease of the lower extremity, with the exception of certain types of pain involving the calf, usually manifests itself distal to or at this level. Consequently, information revealing a decrease in arterial pulsation in this segment is particularly significant. In all the determinations the Boullitte oscillometer was used, the lower edge of the cuff being placed at the base of the internal malleolus and at the wrist joint.

In a series of 86 ratios thus obtained in which the reading at the supramalleolar level was used as the numerator, the lowest value was 1 and the highest 2, which means that in active adults free of vascular disease the magnitude of arterial pulsation in the lower part of the leg is at least equal to and may be greater than that in the lower part of the forearm.

Therefore, if the original premise is correct, that as peripheral arteriosclerotic disease progresses oscillometric readings at any given level in the lower extremities decrease proportionately more than those at any given level in the upper extremities, a point should be reached in the course of the disease at which the magnitude of arterial pulsation in the lower part of the leg becomes less than that in the lower part of the forearm and the ratio becomes less than 1. The corollary of this would be that a ratio less than 1, particularly when accompanied by other evidence of peripheral arteriosclerotic disease, should indicate decreased arterial pulsation in the lower leg, and the actual value of the ratio should be a rough measure of the extent of this decrease.

We therefore applied the ratio in examining a group of patients with arteriosclerotic disease of the lower extremities. This group had the following characteristics in common. All had disability sufficiently severe to have caused their referral to the clinic for persons with peripheral vascular diseases. All were ambulatory and active. In none could pulsations in either the dorsalis pedis or the posterior tibial arteries be felt.

The table presents a compilation of the 30 ratios obtained. All were well under 1, and in 16 instances the oscillometric readings at the supramalleolar level ranged between 1 and 4. An interesting observation is the wide variation in the values of the ratios. Some of the disparity may be due to a factor which we have no way of evaluating, that is, our inability to determine what the ratios were before the arteries became sclerotic. Obviously, to bring his ratio below 1 a person with an originally normal ratio of, say, 1.8 would have to have more severe arteriosclerosis in his lower extremities than a person with an originally normal ratio of 1.2. However, the aforementioned disparity is in line



with the observation we made clinically that the amount of disability suffered by a person with peripheral arteriosclerotic disease is not necessarily proportionate to the decrease in pulsation in the main arterial trunks. The larger vessels may not pulsate at all and still convey enough blood to meet the metabolic demands of the tissues.

Another qualifying factor to be kept in mind, particularly in basing a prognosis on the value of a ratio, is that the test gives information concerning arterial pulsation in the lower part of the leg only. While, as explained, this knowledge is pertinent, nevertheless, a ratio indicating

*Ratio of the Oscillometric Reading at the Lower Part of the Leg to the Oscillometric Reading at the Lower Part of the Forearm in Thirty Cases of Arteriosclerotic Disease of the Lower Extremities*

Type of Sclerosis	Oscillometric Readings		Ratio
	Lower Leg (Numerator)	Lower Forearm (Denominator)	
Senile	00	15	00
Senile	00	45	00
Senile	00	50	00
Diabetic	Trace	40	00
Diabetic	Trace	65	00
Senile	Trace	40	00
Senile	Trace	40	00
Senile	Trace	35	00
Senile	05	40	01
Senile	10	75	01
Senile	05	50	01
Diabetic	05	0	01
Senile	05	20	01
Diabetic	05	30	01
Senile	05	10	01
Senile	15	75	02
Senile	10	50	02
Senile	10	45	02
Senile	10	40	02
Senile	20	65	03
Diabetic	10	30	03
Senile	15	55	04
Senile	35	80	04
Senile	10	20	05
Senile	15	30	05
Senile	15	30	05
Diabetic	25	50	05
Senile	40	80	05
Senile	20	35	05
Diabetic	20	30	06

decreased but still relatively good pulsation in the lower part of the leg might be obtained and yet the patient might have an atheromatous plaque in the popliteal artery which could be the site of a sudden thrombosis, or the digital vessels to one or more toes might be relatively more diseased and suddenly thrombose, or the arteriolar bed might be sclerosed or in a state of spasm.

The practical utility of the test is that it enables the examiner to demonstrate in a roughly quantitative way decreased arterial pulsation in the lower part of the leg. When considered in conjunction with the history and with the results of the physical examination and of studies of the cutaneous temperature, the test assumes real significance.

# PERIARTERITIS NODOSA

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The relative rarity of periarteritis nodosa and the difficulty of recognizing its manifestations during life have brought it to the attention of numerous investigators. That the total number of cases reported is still comparatively small justifies our reporting 6 new cases occurring in recent years at the Peter Bent Brigham Hospital. Two additional cases have been reported previously from this clinic<sup>1</sup>. Thus, of 53,000 patients admitted for medical treatment to the Peter Bent Brigham Hospital since 1913, the diagnosis of periarteritis nodosa has been confirmed in the cases of only 8. It is to be hoped that increasing data may throw some light on the etiology of the disease and perhaps explain some of its bizarre symptomatology. We hope, too, that systematic recording of all the different syndromes that may result from the localization of the vascular process may help to increase the recognition of this disease during life.

## REPORT OF CASES

CASE 1—*A Chinese woman with a history of seasonal allergic rhinitis and clinical evidence of chronic glomerulonephritis, cirrhosis of the liver and healed pulmonary tuberculosis, death from anemia, widespread periarteritis nodosa revealed at autopsy*

From the Renal Clinic and the Medical Service of the Peter Bent Brigham Hospital

Assistance was received from the Fund for Research in Renal and Vascular Disease

1 Bennett, G. A., and Levine, S. A. Two Cases of Periarteritis Nodosa, One with Unusual Manifestations (Meningeal Form), *Am J M Sc* **177** 853 (June) 1929

M C, a 41 year old Chinese housewife, entered the hospital on Aug 29, 1930, with complaints of jaundice and itching of the skin of three weeks' duration. The family history was noncontributory. The patient had had a fever, probably rheumatic, at the age of 19 and seasonal allergic rhinitis since the age of 30. A little over a year prior to entry she had suffered weakness and palpitation. A cough productive of a watery, frothy sputum had been present for over a year. Eight months before admission she vomited bright red blood on several occasions, and progressive loss of weight began. One month before entry shortness of breath, epigastric distress and backache were added to her symptoms. The abdominal pain was intermittent and localized in the epigastrium, with no radiation. About this time swelling of the ankles also appeared. One week later itching of the skin was noted, but obvious jaundice was not present until three days before the patient's admission. A week prior to admission she noted several bloody stools. Acholic stools had never been present. Nausea was present, but there was no recurrence of the vomiting.

Physical examination revealed a well developed but poorly nourished woman with obvious icterus of the skin and sclera. The pupils were slightly irregular, but equal, they were miotic and reacted sluggishly to light (? morphine). Ophthalmoscopic examination disclosed numerous fresh and old hemorrhages, particularly surrounding the maculas. There was dulness on percussion over the apexes of both lungs, elsewhere the note was resonant. Bronchial respiratory sounds were heard over the apexes and the interseapular region on the right. After coughing, fine, dry, subcrepitant rales were noted over these areas. On percussion, the heart was found to be enlarged, and the right border of dulness was noted to be 4 cm to the right of the midsternal line. The apical impulse was felt at the anterior axillary line. A loud, rough systolic murmur was heard over the apex, and just below, a to and fro friction rub. There were no diastolic murmurs. The radial and brachial vessels were markedly thickened and tortuous. The blood pressure with the patient recumbent was 170 systolic and 108 diastolic. The abdomen showed generalized tenderness but no spasm or rigidity. The edge of the liver was not tender and was palpable 2 fingerbreadths below the right costal margin. The spleen was not palpable. The abdominal reflexes were not obtained. Peripheral edema was absent. Deep reflexes were present and active throughout, except for the ankle jerks. There were no sensory changes. No significant adenopathy was discovered. The temperature was normal on admission, but rose to 102 F (rectal) within twelve hours and remained elevated during the rest of the patient's stay in the hospital. The pulse rate varied between 90 and 120 beats. Respirations were normal.

Of the laboratory data, the following were significant: erythrocyte count 2,500,000, hemoglobin 40 per cent (Sahli), and leukocyte count 23,300, with 87 per cent polymorphonuclears, 6 per cent lymphocytes, 6 per cent monocytes and 1 per cent basophils. No eosinophils were seen. Several urinalyses revealed specific gravities of 1.010 to 1.014, with a very slight to a slight trace of albumin, no sugar, and sediments containing rare red and white cells and 1 or 2 small granular casts per high power field. The stool gave a 3 plus reaction to the benzidine test, and stercobilin was present. The icterus index was 25 and the urea nitrogen of the blood 105 mg per hundred cubic centimeters. Culture of the blood was sterile. The vomitus contained free hydrochloric acid. The Wassermann and Hinton reactions were negative.

The patient's course in the hospital was progressively downhill, and she died in coma on September 3, four days after admission. The clinical diagnosis was

the terminal stage of chronic glomerulonephritis, with pericarditis and uremia. The enlarged liver, the absence of any signs of cardiac decompensation and the jaundice suggested additional hepatic involvement, probably cirrhosis. Infestation with some obscure Oriental parasite was also advanced as a possible diagnosis. Old tuberculosis accounted for the findings in the apex of the chest. Thus to explain the bizarre picture at least three diagnoses had to be advanced.

The autopsy revealed pulmonary congestion and edema, cardiac hypertrophy and dilatation, serofibrinous pericarditis, fibrinous pleurisy on the left, generalized arteriosclerosis and arteritis with resultant tissue changes. Gross inspection showed that the hepatic, superior mesenteric, gastric, uterine and renal arteries were involved. The organs most affected were the liver and the kidneys. Many small, purplish, firm nodules were seen beneath the peritoneum, at the attachment of the mesentery to the small intestine. On cross section these nodules showed laminated, antemortem blood clots, which were adherent to the walls of their capsules. The capsules were continuous with the walls of the main arteries. It was interesting that no gross changes were noted in the peripheral, pulmonary or coronary vessels. Microscopic examination disclosed changes in the smaller pulmonary arteries and capillaries consistent with an early stage of acute arteritis. One thrombosed small artery was demonstrated in the spleen. There was evidence of chronic progressive vascular nephritis superimposed on thrombotic changes in the renal vessels. The vessels of the adrenals, urinary bladder, broad ligaments and uterus also were involved in the process. The changes were interpreted as characteristic of periarteritis nodosa.

*CASE 2—A 19 year old Greek student with polyarthritis, unexplained low grade fever, leukocytosis, splenomegaly and cutaneous nodules, periarteritis nodosa shown by biopsy, clinical recovery of four years' duration*

A P, a 19 year old student, entered the hospital for the first time on Jan 5, 1935, complaining of painful joints of five months' duration. The family history was entirely noncontributory. The patient's history was irrelevant. He had been free from symptoms until the onset of the recurrent attacks of articular pains which involved the extremities, starting in the "right foot." Two to three days after the onset the left ankle became involved. Within three weeks both ankles were swollen and painful. In rapid succession the wrists, elbows and fingers became swollen, painful and stiff. A series of intramuscular injections of typhoid vaccine had been given, without relief. Shortly thereafter he entered the hospital. He had lost 70 pounds (31.8 Kg) in the preceding two and a half months.

Physical examination revealed a well developed but poorly nourished youth, apathetic but not acutely ill. Facial pallor was marked, and profuse sweating produced a peculiarly pungent odor. The fundi were entirely normal. The heart was not enlarged, the rhythm was regular, with a rate of 102, there were no thrills, rubs or murmurs. The blood pressure was 120 systolic and 80 diastolic. The liver and spleen were considerably enlarged. There was no peripheral edema. Several enlarged firm lymph nodes were found in the axillary and inguinal regions on both sides. There was diffuse tenderness over most of the muscles. The ankle joints were tender to palpation but were not swollen. The rectal temperature was 101 F.

The laboratory data revealed leukocytosis (18,400 cells), with 76 per cent polymorphonuclears, 23 per cent lymphocytes and 1 per cent eosinophils, the hemoglobin content was 60 per cent (Sahli), and the erythrocyte count 4,900,000, with platelets approximately normal. Urinalyses showed concentrations of 1005

to 1023, with no albumin or sugar and with rare red cells but no casts in the sediment. The Wassermann and the Hinton reaction of the blood were negative. Because of the splenomegaly, anemia, arthritis and fever, diagnoses of undulant fever, rheumatic fever, chronic malaria and Felty's syndrome were first considered. Agglutination reactions with *Bacillus melitensis* were negative. Agglutination with the *Bacillus typhosus* group gave positive results in low titer, probably because of the previous injections of typhoid vaccine. Leukocyte counts varied from 6,000 to 18,000, but the erythrocyte counts remained rather constant. There was a daily elevation of temperature to 99 and 100 F. Salicylates were given, with no appreciable effect on the fever. Electrocardiograms revealed no prolongation of the PR interval. Roentgenograms of the sinuses and teeth showed no evidence of focal infection. Eleven intramuscular injections of typhoid vaccine were given, with good elevations of temperature and some alleviation of the articular symptoms. On February 25 a few small, tender, subcutaneous nodules, about the size of a pea, were felt on the flexor surface of the left forearm. With cessation of the injections of typhoid vaccine, the patient complained of the recurrence of articular pains. New crops of subcutaneous nodules appeared, with surrounding areas of induration about 2 cm in size. These were considered to be lesions of erythema nodosum or the subcutaneous nodules of rheumatic fever. Unfortunately, a biopsy of one of the cutaneous lesions was not done. The patient was discharged on March 23.

He reentered the hospital on Oct 28, 1935, with similar complaints of generalized weakness and intermittent pain and tenderness in the muscles and joints, especially those of the lower extremities. Against advice given him at the time of his discharge, he had been ambulatory during the interim. He had entered another hospital during the period, where the results of biopsy of one of the nodules had been reported as "suggestive of periarteritis nodosa." The clinical diagnosis, however, was uncertain when he was discharged from the hospital, against advice. In July he was seized by a vague, severe midabdominal "cramp," which was non-radiating in character but severe enough to double him up. There was no nausea, vomiting, constipation, diarrhea, dysuria, urinary frequency, jaundice or costovertebral pain. The pain disappeared spontaneously after several days. During the ten days prior to entry the patient had noted numerous erythematous, circinate lesions over the trunk and extremities. These were about 2 cm in diameter and were elevated, they were not tender, but on palpation were found to be indurated. They appeared principally over the anterior and the posterior part of the thorax and the upper parts of the arms. Although weakness and sweating persisted, the patient had regained 25 (11.3 Kg) of the 70 pounds (31.8 Kg) he had lost.

Physical examination gave essentially the same results as on his previous admission. The temperature was 98.6 F, the pulse rate was 96, and his blood pressure was 105 systolic and 65 diastolic. The edge of the liver was just palpable below the right costal margin. The firm, rounded edge of the spleen could be felt 4 fingerbreadths below the left costal margin. There was no lymphadenopathy.

The laboratory data revealed an erythrocyte count of 5,300,000 with 68 per cent hemoglobin (Sahli) and a leukocyte count of 9,800. There was 75 per cent polymorphonuclears and 25 per cent lymphocytes in the differential count. No eosinophils were found. The Wassermann and the Hinton reaction of the blood and the results of analyses of the stool and urine were again negative. Roentgenograms of the chest revealed only increased hilar shadows and pulmonary markings, compatible with chronic bronchitis. Biopsy of a subcutaneous nodule showed

two large arteries in which the lumens did not appear narrowed. There was evidence of intimal proliferation. The media was infiltrated with lymphocytes and mononuclears but showed little degeneration or fibrosis. The adventitia showed a marked reaction (fig 1), with infiltration of lymphocytes, mononuclear cells and, rarely, plasma cells. A few polymorphonuclear leukocytes also were seen. A careful search for bacteria or inclusion bodies was without avail. There were no aneurysmal dilatations. There was no capsule about the nodule. The pathologic diagnosis was "periarteritis nodosa."

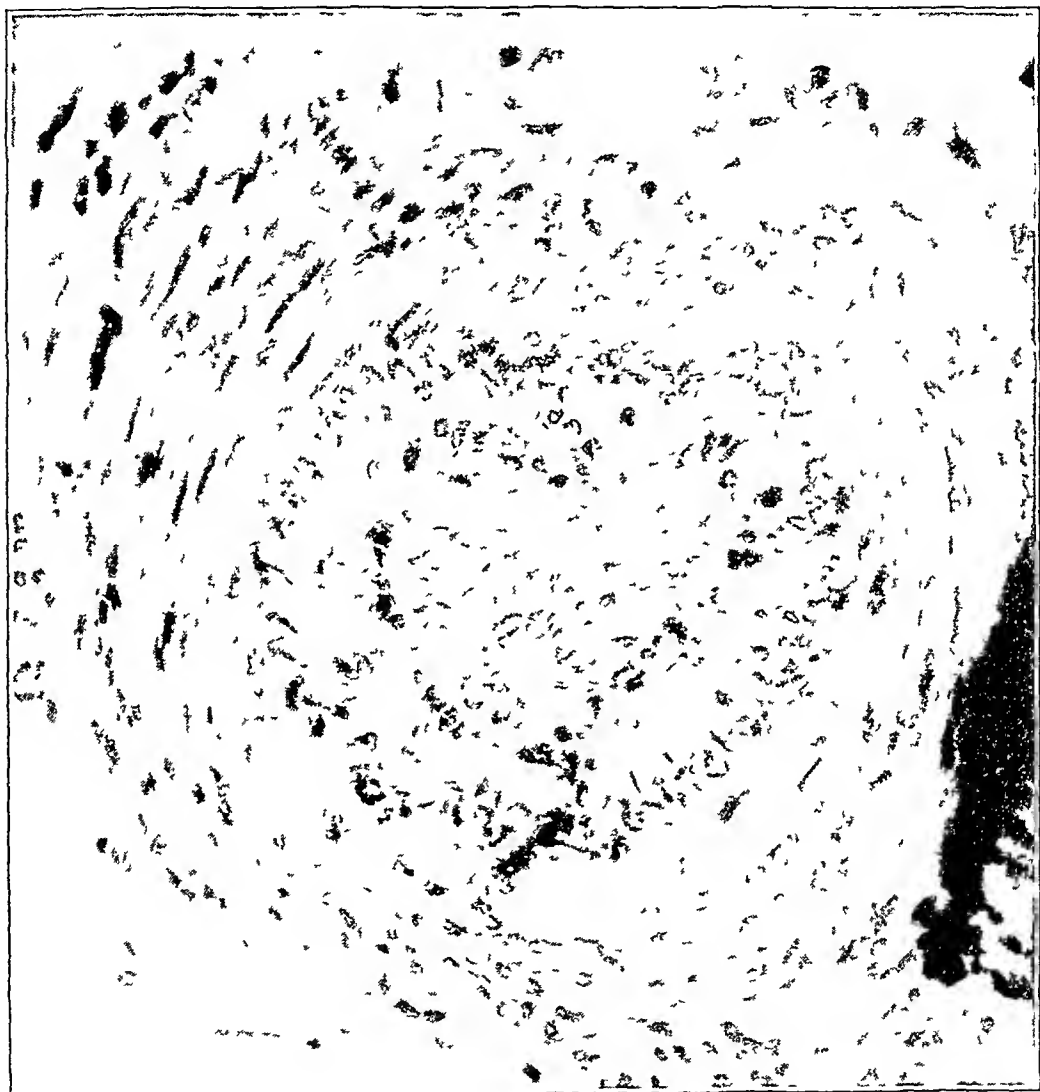


Fig 1 (case 2)—A small artery from the subcutaneous tissue removed for biopsy. The intimal thickening is considerable. About the vessel are numerous lymphocytes and mononuclear cells. In other places these inflammatory cells were seen within the wall of the vessel (magnification,  $\times 650$ ).

After discharge from the hospital, the patient went to Florida, returning in April 1938. Examination disclosed no deviation from the normal, the liver and spleen no longer being palpable. There were no cutaneous lesions, and the blood pressure, the composition of the urine and the blood count were within normal limits. The patient had regained his lost weight and suffered no chills or fever. At present (August 1938) he is up and about and leads a normal existence.

CASE 3—*A surgeon, presenting a vague picture of physical exhaustion, arthritis, fever, tachycardia, leukocytosis and rapidly appearing hypertension, with development of typical anginal attacks, peculiar neurologic findings and signs of glomerulonephritis, clinical diagnosis of periarteritis nodosa, confirmed by necropsy*

T E C, a 56 year old surgeon, entered the hospital in September 1936, complaining of weakness, chills and fever of five weeks' duration. He complained also of arthritic pains, marked exhaustion and several attacks of irregular cardiac action. There were no other systemic complaints. His personal and his family history were irrelevant.

Physical examination revealed a pale, nervous, middle-aged man in a state of physical exhaustion. The skin was cold and clammy. Ophthalmoscopic examination gave normal results. Except for periods of paroxysmal auricular fibrillation, the heart appeared normal on auscultation, with no murmurs. There were a few moist rales over the base of the left lung. The abdominal examination gave normal results. There was no peripheral edema. The deep reflexes were active. There was marked hypesthesia over the lateral surfaces of both legs, with loss of the postural and the vibratory sense in the lower extremities. The blood pressure was 118 systolic and 80 diastolic. The two most significant signs were a low grade, intermittent fever, which continued throughout the patient's stay in the hospital, and leukocytosis (15,000 cells), with 95 per cent polymorphonuclears. There were no eosinophils. Urinalysis repeatedly gave normal results. The serologic reactions were negative. The spinal fluid was normal with no cells and normal dynamic readings. Chemical studies of the blood furnished no clue to the diagnosis. Agglutinations against B typhosus, B melitensis, Proteus X19 and the gonococcus gave negative results. Smears for malarial parasites were negative. Searches for hidden focal infection gave negative results. Cultures of the blood were sterile. The patient was finally allowed to leave the hospital for convalescence at home, no definite diagnosis having been made.

He reentered the hospital on November 30. In the interim he had been bed-ridden, and he now presented new complaints—tingling and numbness of the hands, as well as frequency and urgency of urination. Papilledema of the right nerve head and slight blurring of the left optic disk suggested the possibility of a brain tumor. Roentgenograms of the skull were considered to show no abnormality. The heart was now enlarged to the left, and there was a soft, blowing systolic murmur at the apex. The blood pressure was 120 systolic and 80 diastolic. The lungs were clear. Neurologic examination revealed atrophy of the intrinsic muscles of the hands, with ulnar, median and radial palsies. Cystoscopic examination, made because of difficulty in voiding, revealed only benign enlargement of the prostate. Roentgen studies of the gastrointestinal tract revealed nothing abnormal. Two observers thought the patient had periarteritis nodosa because a number of systems were involved. The intermittent fever continued, and the secondary anemia progressed. The patient was discharged from the hospital on December 5 and was followed at home. Typical anginal attacks soon developed, and later heart failure with pleural effusion required three thoracenteses. The fluid removed had the characteristics of a transudate. The blood pressure rapidly rose to 190 systolic and 110 diastolic, and though originally urinalyses had given normal results, subsequent ones revealed increasing amounts of albumin, red cells and hyaline casts. The urea nitrogen of the blood rose to 59 mg per hundred cubic centimeters and the nonprotein nitrogen to 107 mg. Several weeks before the patient died a few nodules appeared in the skin of the left forearm, making the clinical diagnosis seem more certain. He died suddenly on March 8, 1937.

Autopsy disclosed that the immediate cause of death was bronchopneumonia. Gross examination disclosed two small aneurysmal dilatations of the mesenteric arteries, but histologic examination revealed lesions of periarteritis nodosa distributed widely. Those in the pericardium, peripheral nerves (fig 2) and voluntary muscles were characteristic of the disease as usually described in the literature. The lesions in the peripheral nerves were acute. However, in the mesentery, the kidneys and elsewhere the lesions were apparently much older, with marked concentric thickening of the intima. The pathologist was uncertain whether the latter changes could be called healed lesions of periarteritis nodosa or atypical vascular lesions. Thus it was thought that in this case the various stages of the disease were well demonstrated.

The patient, who was considered by many to be psychoneurotic during the early course of his illness, presented marked loss of weight, chills and fever, paroxysmal

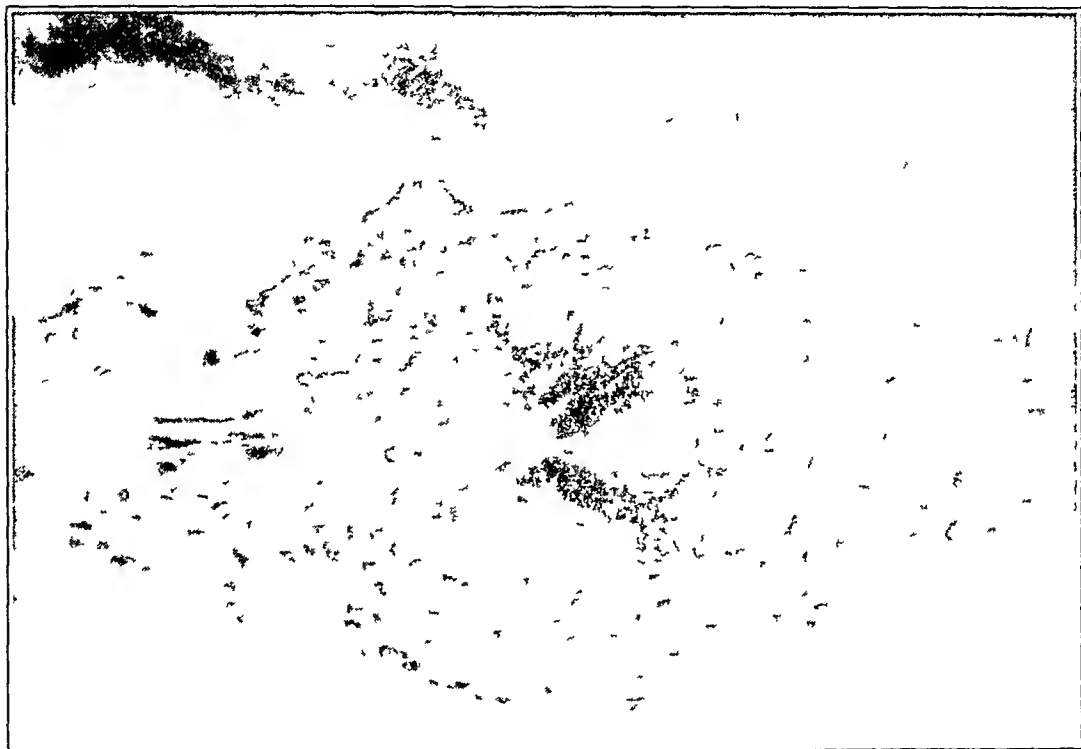


Fig 2 (case 3)—A small arteriole adjacent to the sciatic nerve, the fibers of which are shown at the top of the illustration. Deep-staining necrotic material is present in the wall. All layers are heavily infiltrated with lymphocytes and mononuclear cells (magnification,  $\times 490$ ).

fibrillation, hydrothorax and peripheral neuritis. Signs and symptoms of nephritis, with hypertension and papilledema, as well as angina pectoris, later developed. A clinical diagnosis of periarteritis nodosa was made and confirmed by autopsy, which revealed that the condition involved vessels of the heart, gastrointestinal tract, mesentery, liver, kidneys, testes, peripheral nerves, voluntary muscles, spleen and prostate.

*CASE 4—A woman with signs of hypertrophic arthritis, emphysema and chronic myocarditis, death from congestive heart failure with bronchopneumonia widespread periarteritis nodosa revealed by autopsy.*



S G, a 61 year old Russian housewife, entered the hospital on Dec 30, 1936, complaining of pain in the shoulders and hips of one month's duration. Other than a slight productive cough of twenty years' duration, she could remember no previous symptoms. The pains in the shoulders and hips were described as sticking, knifelike, nonradiating and exaggerated by motion. There were no complaints of chills, fever or sweats, but the patient had noticed occasional palpitation over the heart, shortness of breath on exertion, malaise and weakness. For the two weeks preceding her entry progressive swelling of the ankles and orthopnea also were noted.

Physical examination revealed a small, emaciated, elderly woman in moderate respiratory distress with marked cyanosis. Examination of the head revealed no deviation from the normal. Numerous fine, sticky rales were heard over the bases of both lungs, but the percussion note was resonant throughout and whispered voice was normally transmitted. The heart was enlarged to the left. The heart sounds, although somewhat distant and rapid, were regular. No murmurs or rubs were heard. The blood pressure was 150 systolic and 100 diastolic. Abdominal examination did not disclose masses or tenderness. Abduction of the shoulders was markedly limited. Many of the small joints of the hands, the wrists and the left elbow were tender on palpation. There was moderate pitting of the ankle with sacral edema. The temperature was 100 F on admission and returned to normal after the fourth day in the hospital. The pulse rate was 104 and the respiratory rate 24. Urinalyses revealed concentrations of 1030, with no albumin or sugar. The sediment contained occasional hyaline and several granular casts with no red or white blood cells. The hemoglobin content was 90 per cent (Sahli), the erythrocyte count 5,000,000 and the leukocyte count 12,800, with 71 per cent polymorphonuclears, 29 per cent lymphocytes and no eosinophils. The Wassermann and Hinton reactions of the blood were negative. Examinations of the stool revealed nothing abnormal. Despite supportive treatment, the patient became progressively weaker and died on the sixth day after entry.

No suspicion of periarteritis nodosa was entertained, the clinical diagnoses being bronchopneumonia, chronic myocarditis, hypertrophic arthritis, pulmonary emphysema, chronic bronchitis and generalized arteriosclerosis. Not until the microscopic sections were prepared was the underlying process determined.

Autopsy revealed bilateral bronchopneumonia with acute fibrinous pericarditis. Gross examination was not conclusive, but histologic examination of most of the organs, especially of the skeletal muscles, showed changes typical of periarteritis nodosa. The lungs, spleen, accessory spleen, pancreas, liver, kidneys, periadrenal tissue, uterus and skeletal muscles were involved.

*CASE 5—A mill worker with fever, foot drop, wrist drop and signs of chronic glomerulonephritis, death from bronchopneumonia, periarteritis nodosa disclosed by autopsy*

C A W, a 63 year old white mill foreman, entered the hospital on March 31, 1937, complaining of progressive weakness and loss of weight of one year's duration. His family history and personal history were noncontributory. Because of weakness he was forced to stop work in January. Two weeks later he entered a hospital, with edema of the ankles and palpitation. A letter from his local physician stated he had found "moderate emaciation, normal pupillary reaction, a small hemorrhage in the right retina, a grade 1 systolic murmur over the base of the heart, crackling rales at the bases of both lungs and a blood pressure of 120 systolic and 90 diastolic. The liver and spleen were not enlarged, the ankles

were slightly edematous, neurologic findings were normal except for a weak response of the quadriceps femoris muscle. Roentgen studies of the gastrointestinal tract revealed no abnormality. Lumbar puncture gave normal results except for absence of response to unilateral jugular compression, but a good rise in pressure followed bilateral compression." In the two weeks preceding entry the patient had become drowsy, markedly constipated and incontinent of urine and feces. Anorexia was marked. He had lost over 30 pounds (13.6 Kg) in the preceding year.

Physical examination revealed a confused, delirious man without obvious respiratory embarrassment. There were spasmodic muscular twitchings and gross tremors of the arms and legs. The pulse was regular, with a rate of 120. The temperature was 101.3 F and the respiratory rate 26 per minute. Heart sounds were distant, and no murmurs or rubs were heard. The blood pressure was 150 systolic and 90 diastolic. There was bilateral wrist and foot drop, but the deep reflexes were intact and there were no abnormalities of sensation. There was no peripheral edema.

Urinalysis showed 10 to 15 erythrocytes with a few hyaline and granular casts and no albumin or sugar. The hemoglobin content was 88 per cent (Sahli), the erythrocyte count 5,500,000 and the leukocyte count 17,600, with 92 per cent polymorphonuclears and no eosinophils. The serologic reactions were negative. The urea nitrogen of the blood was 30 mg per hundred cubic centimeters and the total protein 5.3 Gm per hundred cubic centimeters, with 2.2 Gm of albumin and 3.1 Gm of globulin. The spinal fluid was clear, with normal dynamic readings and laboratory findings. The clinical course in the hospital was progressively downhill, and death occurred on the third day in the hospital.

This case was another in which the patient presented a multiplicity of symptoms which could not be put in one category clinically and the typical arterial changes appeared only in the microscopic sections. The clinical diagnoses were chronic glomerulonephritis and polyneuritis on an avitaminotic basis. Lead poisoning also had been suggested.

Autopsy disclosed bronchopneumonia and several incidental gross changes. The nature of the underlying lesion was not evident until the microscopic sections were examined. These showed acute and extensive lesions of periarteritis nodosa included in the heart, gastrointestinal tract, pancreas, mesentery, gallbladder, kidneys, periadrenal tissue, urinary bladder, prostate, seminal vesicles and testes. The arterial lesions were associated with acute necrosis of the various organs.

*CASE 6—A fireman with a verified gastric ulcer and macroscopic hematuria, death from uremia with pericarditis, widespread periarteritis nodosa and carcinoma of the stomach revealed by autopsy.*

J. M., a 64 year old fireman, entered the hospital on March 7, 1938, complaining of intermittent epigastric pain. His family history and personal history were noncontributory except that he had had sore joints from the age of 15. The soreness had not been severe enough to confine him to bed. There was no history of allergy. He admitted having taken five or six glasses of ale daily for years. He stated he was well until one year prior to entry. At that time he began to notice gnawing pain in the epigastrium, which radiated through to the back but not to either flank. The pain came on one to four hours after meals and at first was partially relieved by alkalis and food. Although mild at the onset, the pains sometimes doubled him up. About eight weeks prior to entry he visited his family physician and was placed on an "alkaline regimen" and liquid diet. This

gave no relief, and soon anorexia developed, with nausea at the sight of food. There were occasional vomitings of clear, watery phlegm. He did not suffer diarrhea, hematemesis or melena and had never noticed clay-colored stools or jaundice. For over a year he had noticed that his urine seemed "very red." On several occasions blood clots were passed, with no attendant dysuria. There was no history of retention of urine, incontinence, diminution in the force of the stream or pyuria. He had urinated once during the night for the preceding six months. The patient had never noticed any swelling of the ankles. He stated that he had lost about 15 pounds (6.8 Kg) in the preceding four weeks.

Physical examination revealed an undernourished, wasted man, lying quietly in bed, somewhat drowsy but oriented. The temperature was 98.6 F, the pulse rate 76 and the respiratory rate 20 per minute. The breath was urinous. There was no pallor or cyanosis. Over the shoulders and back was an acneiform eruption, and in both axillae were red macular patches. The tonsillar pillars, as well as the posterior part of the pharynx were beefy red. The heart appeared normal in size on percussion and presented no thrills or murmurs. The peripheral vessels were somewhat thickened, and the blood pressure was 155 systolic and 95 diastolic. The chest was hyperresonant, but auscultation revealed nothing abnormal. The abdomen exhibited voluntary muscular rigidity, most marked in the epigastrium. On palpation the edge of the liver was found to be firm, smooth and tender. No other organs were palpable. The deep reflexes were physiologic, but the Babinski phenomenon was present on the left. There was no peripheral edema. Ophthalmoscopic examination revealed only moderate arteriovenous nicking.

Laboratory findings included an erythrocyte count of 4,100,000, with 85 per cent hemoglobin (Sahli), and a leukocyte count of 14,000, with 85 per cent polymorphonuclears, 2 per cent eosinophils and 13 per cent lymphocytes. Urinalysis showed a concentration of 1012, with a slight trace of albumin and sediment loaded with hyaline and fine brown granular casts; there were 3 to 5 red and 1 to 2 white blood cells per high power field. The excretion of phenolsulfonphthalein was 20 per cent. The urea nitrogen of the blood was 77 mg per hundred cubic centimeters on admission and rose progressively to 136 mg. The icterus index was 6. The stool gave positive reactions to the benzidine test for blood. Analysis of specimens of vomitus showed 30 degrees of free hydrochloric acid. A series of examinations of the gastrointestinal tract revealed a constant, irregular filling defect involving the antral third of the stomach, with a crater 2 cm in diameter along the lesser curvature. This was interpreted as a benign peptic ulcer. The rest of the tract was normal. Examination of the genitourinary tract revealed a sessile papilloma of the bladder about 3 cm in diameter. This was not considered malignant, and fulguration was carried out through the cystoscope. Several days after admission a blotchy, red, maculopapular eruption appeared and became rapidly generalized, associated with moderate pruritus. When medication with barbiturates was discontinued, the rash only partially disappeared. After several days the temperature became as high as 103 F, dropping terminally. During the last forty-eight hours of his illness the patient exhibited marked restlessness, twitching and anuria. A loud pericardial friction rub was heard just before death, on the thirteenth day in the hospital.

Autopsy revealed multiple septic infarcts of the kidneys, hypertrophy of the heart with pericarditis, an area of ulceration on the lesser curvature of the stomach, which showed carcinomatous changes, and a benign papilloma of the bladder.

Microscopic examination showed disseminated periarteritis nodosa, involving the heart, spleen, stomach, jejunum, pancreas, liver, gallbladder, kidneys, ureters, urinary bladder, prostate, testes, adrenals and thyroid. Giemsa's and Levaditi's stains disclosed neither organisms nor spirochetes.

Thus, in a case in which the gastric and renal symptoms dominated the condition terminated in uremia with pericarditis. Clinical diagnoses were unsatisfactory in explaining all the symptoms presented. Autopsy revealed involvement of most of the organs of the body by the arterial lesions.

Analyzing these cases for frequency of symptoms and signs, one notes that fever was the only constant finding in the series. Loss of weight, weakness, edema, leukocytosis and hypertension occurred in 5 cases, and dyspnea, cough, abdominal pain, anemia, emaciation, albuminuria and hematuria appeared in 4 of the 6 cases. A summary of the other findings may be seen in table 1.

TABLE 1—*Frequency of Symptoms and Signs in the Present Series of 6 Cases of Periarteritis Nodosa*

Disturbance	Frequency	Disturbance	Frequency
Fever	6	Arthritis	3
Loss of weight	5	Atrophy	2
Edema	5	Vomiting	2
Weakness	5	Cyanosis	2
Leukocytosis	5	Visual disturbance	2
Hypertension	5	Neuritis	2
Dyspnea	4	Nodules	2
Emaciation	4	Headache	1
Cough	4	Nausea	1
Abdominal pain	4	Convulsions	1
Albuminuria	4	Pain in the chest	1
Hematuria	4	Purpura	1
Anemia	4	History of allergy	1
Rapid onset	3	Vertigo	0
Icterus	3	Eosinophilia	0
Sensory involvement	3		

#### REVIEW OF THE LITERATURE

Credit is usually given to Kussmaul and Maier<sup>2</sup> for their description of periarteritis nodosa in 1866. However, it is of historical interest that Rokitansky<sup>3</sup> first described the macroscopic lesion in 1852, under the title "The Formation of Aneurysms of the Arteries in General, Except the Aorta and Most of Its Primary Branches, with the Further Exception of the Cerebral Arteries." Thirty-five years later Eppinger<sup>4</sup>

2 Kussmaul, A, and Maier, R. Ueber eine bisher nicht beschriebene eigen-thumliche Arterienerkrankung (Periarteritis nodosa), die mit Morbus Brightii und rapid fortschreitender allgemeiner Muskellahmung einhergeht, Deutsches Arch f klin Med **1** 484, 1866.

3 von Rokitansky, C. Ueber einige der wichtigsten Erkrankungen der Arterien [table 6], Denkschr d k Akad d Wissensch **4** 49, 1852.

4 Eppinger, H. Pathogenesis (Histogenesis und Aetiologie) der Aneurysmen einschliesslich des Aneurysma equi verminosum, Arch f klin Chir (supp) **35** 1, 1887.

reviewed the microscopic sections and confirmed the diagnosis. There is some reason for believing that the disease was recognized as early as 1755 by Michaelis and Matani<sup>5</sup> and again in 1810, by Pelletan,<sup>6</sup> who reported briefly a case in which he counted sixty-three small aneurysms of various arteries. It is of interest that Kussmaul and Maier first thought their patient had trichinosis.

Reviewing the world literature, one finds but 38 cases up to 1914, including 5 from the United States.<sup>7</sup> The first American reports were those of Dickson<sup>8</sup> in 1907 and Longcope<sup>9</sup> in 1908. In 1928 Strong<sup>10</sup> collected 21 cases from the journals published in English, and Curtis and Coffey<sup>11</sup> found but 38 cases up to and including 1933. Of these the diagnosis was made ante mortem in only 3. The total number of case reports that have reached the world literature up to June 1938 is slightly over 300, according to a check of the *Quarterly Cumulative Index Medicus* and the "Index-Catalogue of the Library of the Surgeon General's Office."

Reviewing the isolated case reports in the literature, we noted that since the survey of Gruber,<sup>12</sup> in 1926, no complete resumé of the literature, English or foreign, has appeared. The two surveys most often quoted are those of Strong (1928)<sup>10</sup> and of Curtis and Coffey (1934).<sup>11</sup> Strong tabulated the incidence of involvement of the major organs as well as the frequency of hypertension, asthma and arthritis in his 21 cases. Curtis and Coffey omitted the same data from their report of 17 collected cases, but added an analysis of most of the common symptoms and signs occurring in their series, to produce a much more comprehensive chart. Unfortunately, they did not tabulate all of the same data for the 21 cases previously collected by Strong. As a result, the combined chart gives one an erroneous impression of the frequency of the various symptoms and signs in the total series. Since the report

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5 Michaelis and Matani (1755), cited by Eppinger<sup>1</sup> and by Schreiber, R. Ueber Poliarteritis nodosa, Inaug. Dissert., Königsberg, O. Kummel, 1904.

6 Pelletan, P. J. Clinique chirurgicale, ou memoires et observations de chirurgie clinique, et sur d'autres objets, relatif a l'art de guerir, Paris, J. G. Denter, 1810, vol. 1.

7 Lamb, A. R. Periarteritis Nodosa—A Clinical and Pathological Review of the Disease, with a Report of Two Cases, Arch. Int. Med. **14** 481 (Oct.) 1914.

8 Dickson, W. E. C. Polyarteritis Acuta Nodosa and Periarteritis Nodosa, J. Path. & Bact. **12** 31, 1907.

9 Longcope, W. T. Periarteritis Nodosa, with a Report of a Case with Autopsy, Bull. Ayer Clin. Lab., Pennsylvania Hosp. **12** 60, 1908.

10 Strong, G. F. Periarteritis Nodosa, with Report of a Case, Canad. M. A. J. **19** 534 (Nov.) 1928.

11 Curtis, A. C., and Coffey, R. M. Periarteritis Nodosa. A Brief Review of the Literature and a Report of One Case, Ann. Int. Med. **7** 1345 (May) 1934.

12 Gruber, G. B. Kasuistik und Kritik der Periarteritis nodosa, Zentralbl. f. Herz- u. Gefasskr. **18** 198, 1926.

by Curtis and Coffey, in 1934, 57 more cases have been reported in the English literature up to June 1, 1938. If we were to add our 6 cases, the number of acceptable cases in the English literature would total 101. Fortunately, the case reports in the English literature, with 3 exceptions, have been outlined in great detail. On the other hand, many of the foreign reports were not acceptable for analysis, because of the lack of pathologic verification. Because of the various synonyms that have been applied to periarteritis nodosa by many pathologists, a search of the foreign literature has been unsatisfactory. Believing the 101 cases reported in the English literature to be a statistically significant number, we have restudied the entire series, tabulating (table 3) the frequency of the various symptoms, signs and laboratory findings as they appeared in the various case reports.<sup>13</sup> Realizing the bizarre forms the clinical picture of periarteritis nodosa might assume, we made it our basic purpose in assembling such a chart, now that a sufficient number of cases have been reported, to develop a composite picture of the condition. It was hoped that certain features would be more or less characteristic and that more frequent clinical recognition of the disease thus be allowed. The remainder of this report deals with our analysis and summary of the data compiled from the study of the 101 case reports.

#### ETIOLOGIC FACTORS

Various theories concerning the agent causing periarteritis nodosa have been presented. The suggestions include *Spirochaeta pallida*,<sup>14</sup> streptococcic infection,<sup>15</sup> virus infection<sup>16</sup> and parasitic invasion,<sup>17</sup> and

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13 Thus, our chart resembles that of Curtis and Coffey closely in form but has additional columns for recording hypertension, arthritis and history of allergy, as well as for recording the involvement of the major organs noted at necropsy. We have omitted the nervous and cutaneous systems purposely, because of the exceedingly meager reports of their examination. For purposes of publication, it was necessary to report only the totals for the various data. These appear in tables 2 and 3. Throughout the remainder of this report we shall refer to these totals in terms of their frequency of appearance in the 101 original case reports, unless the reference is otherwise qualified.

14 (a) Kussmaul and Maier.<sup>2</sup> (b) Chvostek and Weichselbaum, A. Herdweise syphilitische Endarteritis mit Aneurysmenbildung, *Allg Wien med Ztg* **22** 257, 1877. (c) Versé, M. Periarteritis nodosa und Arteritis syphilitica cerebialis, *Beitr z path Anat u z allg Path* **40** 409, 1907.

15 Klotz, O. Periarteritis Nodosa, *J M Research* **37**:1 (Sept) 1917.

16 (a) von Haun, F. Patho-histologische und experimentelle Untersuchungen über Periarteritis nodosa, *Virchows Arch f path Anat* **227** 90, 1920. (b) Harris, W. H., and Friedrichs, A. V. The Experimental Production of Periarteritis Nodosa in the Rabbit, with a Consideration of the Causal Excitant, *J Exper Med* **36** 219 (Aug) 1922.

17 Cameron, H., and Laidlaw, P. P. Case of Periarteritis Nodosa, *Guy's Hosp Rep* **69** 159 1918.

Recently an allergic reaction<sup>18</sup> has been postulated. The last theory is somewhat distinct from the earlier theories of hyperergy<sup>19</sup>. Suffice it to say that no conclusive evidence with confirmation has been brought forward to substantiate any of these theories. In only 1 of our cases, case 2, was any attempt made to recover or demonstrate the etiologic agent other than by routine antemortem and postmortem cultures of the blood. In this case the condition was recognized during life, and the patient's blood was injected into a guinea pig. Neither a febrile response nor any vascular lesions were subsequently noted. With such meager experimental data as that which we have obtained and that found in the literature, only the morphologic appearance of the tissue and the clinical course remain as a basis for speculations on the causation and nature of the process. The histologic appearance in several of our cases strongly suggested the type of reaction occurring in the vessels in the rickettsial diseases. Numerous attempts with appropriate stains, however, have failed to reveal Rickettsia bodies. No Aschoff bodies were seen in any of our cases. The clinical course was that of a generalized infectious process producing toxemia. The infrequency of pains in the joints and of further manifestations of arthritis in the 101 cases can only be emphasized. The relatively low frequency of a history of allergy, 15 per cent in the series, does not help us to place much faith in the theory of Cohen and others<sup>18</sup> that the lesions are the result of an irreversible allergic process involving the walls of the vessels. This theory suffers also from the fact that as yet no uniform histologic picture exists that would enable the pathologist to state that the lesion is allergic in nature. We are forced to conclude that no acceptable etiologic agent for periarteritis nodosa has yet been demonstrated.

#### PATHOLOGIC PICTURE

On the other hand, the pathologic character of periarteritis nodosa has been well established. According to Arkin,<sup>20</sup> one may divide the lesions into four stages: a degenerative stage, an acute inflammatory stage, a stage of granulation tissue and a so-called healed stage. Periarteritis nodosa involves the middle-sized arteries and arterioles. In the acute form the process has the appearance of an acute inflammatory reaction, involving one or all of the coats of the vessel. For the most part this reaction is distributed over segments of a vessel, the intervening

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18 Cohen, M. B., Kline, B. S., and Young, A. M. The Clinical Diagnosis of Periarteritis Nodosa, *J. A. M. A.* **107** 1555 (Nov. 7) 1936.

19 Gruber, G. B. Zur Frage der Periarteritis nodosa, *Virchows Arch. f. path. Anat.* **258** 441, 1925.

20 Arkin, A. A Clinical and Pathological Study of Periarteritis Nodosa. *Am. J. Path.* **6** 401 (July) 1930.

segments being spared, as emphasized by Kernohan and Woltman<sup>21</sup> In many instances the reaction is confined to but one portion of the circumference of the vessel, but the wall may be involved completely After the acute inflammatory reaction subsides, the polymorphonuclear leukocytes and scattered eosinophils are greatly outnumbered or entirely replaced by lymphocytes and monocytes, and at times by plasma cells In the reparative stage the degree of fibroblastic proliferation varies, and on this variance apparently depends the formation of the small aneurysmal dilatations that are so conspicuous grossly in some instances In other words, it is the lack of fibroblastic proliferation in such areas of weakness that allows for the dilatation and the formation of aneurysm Where the intima is involved thrombi form (fig 2), resulting in infarction of the area supplied by the involved vessel These thrombi may form slowly, organize and become recanalized If so-called healing occurs, there is marked cicatrization, resulting in thickening of the walls of the vessel and narrowing of the lumen The appearance of

TABLE 2—*Involvement of the Major Organs in 87 Cases of Periarthritis Nodosa in Which Autopsy Was Performed*

Organ	Frequency	Percentage
Kidneys	76	87
Heart	73	84
Liver	62	71
Spleen	27	31
Lungs	22	25

the lesions may vary in age and degree of involvement in different places in the same person, and in any given area one may see several stages of inflammation and repair blending together The 87 cases in which autopsy was done collectively yielded examples of these changes, but all stages of the process were rarely shown in a single case

Analyzing the involvement of the major organs, as noted in the 87 complete necropsies (table 2), we found that the organs in the order of their frequency of involvement were the kidneys, heart, liver, spleen and lung

#### CLINICAL SYMPTOMS AND SIGNS

Inspection of table 3 discloses the following salient features in the 101 cases reviewed Males outnumbered females in a ratio of approximately 3 to 1 The ages of the patients varied considerably, ranging from 6 to 71 years,<sup>22</sup> with an average of 36.9 years In 58 cases the onset

21 Kernohan, J. W., and Woltman, H. W. Periarthritis Nodosa. A Clinicopathologic Study with Special References to the Nervous System, *Arch. Neurol. & Psychiat.* **39**: 655 (April) 1938

22 Lamb<sup>7</sup> recounted a verified case from the European literature which involved a 2½ month old infant



was rapid. The complete series shows an average duration of eight and six-tenths months from the beginning of symptoms until death. In the fatal cases, the longest durations were reported by Carr<sup>23</sup> (six years), Arkin<sup>20</sup> and Troutman<sup>24</sup> (four years).

The order of frequency of the more significant symptoms and signs was as follows: fever, leukocytosis (10,000 to 54,000 cells), albuminuria, rapid onset, abdominal pain, edema, loss of weight, hematuria and neuritis. In segregating groups of symptoms or signs as they might occur with vascular involvement of the various organs, we found that albuminuria occurred in 64 per cent of the cases and was associated with other signs of renal damage, such as hematuria and cylindruria, in 46 per cent of the cases. Hypertension occurred in 64 per cent of the cases in which a statement of the blood pressures was recorded. Abdom-

TABLE 3—*Frequency of Symptoms and Signs in 101 Cases of Periarteritis Nodosa*

	Frequency		Frequency
Fever	80	Headache	29
Leukocytosis	70	Arthritis	27
Albuminuria	65	Atrophy	25
Rapid onset	58	Visual disturbances	23
Abdominal pain	57	Purpura	22
Edema	52	Cyanosis	21
Loss of weight	48	Eosinophilia	19
Neuritis	48	Nausea	17
Hematuria	47	Nodules	16
Hypertension*	46	Pain in the chest	16
Dyspnea	41	History of allergy	15
Weakness	41	Convulsions	15
Emaciation	36	Icterus	12
Cough	36	Vertigo	8
Vomiting	31	Positive serologic reaction	8
Sensory involvement	31		

\* Since sphygmomanometric readings were not reported in the general literature before approximately 1915, we believe it justifiable to correct the percentage to 64 per cent.

inal pain occurred in 27 cases and was associated with icterus in 12 instances. Vomiting was noted in 31 cases, nausea, in 17 cases. Thoracic pain occurred in 36 instances and dyspnea in 41. Cyanosis was recorded in but 21 cases. Edema, however, usually of cardiac distribution, was commented on in 52 cases.

With reference to cerebral manifestations, headache was present in 29 cases, vertigo in but 8 instances and convulsions in 15 cases. Visual disturbances were present in 23 cases. Peripheral manifestations were more frequent, neuritis appearing in 48 cases, involvement of sensory nerves in 31 instances and atrophy of various muscle groups, usually the intrinsic muscles of the hands or feet, in 25 cases. Cutaneous manifestations in the form of nodules appeared in only 16 cases. Purpuric

23 Carr, J. G. Periarteritis Nodosa, *M. Clin. North America* **13** 1121 (March) 1934.

24 Troutman, W. B. A Case of Periarteritis Nodosa with Autopsy Findings, *Kentucky M. J.* **29** 144 (March) 1931.

manifestations were present in 22 cases, and various other dermatoses appeared in individual cases

General manifestations of toxemia or sepsis were represented in a high percentage of the cases. Fever was the most frequent sign, occurring in 79 cases. Weakness was noteworthy in 41 cases, emaciation, in 36. Leukocytosis appeared as the second most common finding, being present in 70 cases. Eosinophilia occurred in 19 cases. Anemia, although not recorded in table 2 because of the inexact methods of recording in the case reports, appeared in well over half the cases. Positive serologic reactions of the blood were found in only 8 cases. A history of allergy was obtained in 15 cases, and arthritis was specifically mentioned in 27 cases.

#### DIAGNOSIS

The report of Curtis and Coffey, in 1934, contained but 3 cases in which diagnosis was made ante mortem. To assist in making a correct antemortem diagnosis, many authors have attempted to coordinate the various diagnostic combinations of symptoms and signs that appear in the disease. For many years Meyer's<sup>25</sup> triad, "chlorotic marasmus, polymyositis and polyneuritis and gastrointestinal symptoms," later augmented by Brinkmann,<sup>26</sup> and Christeller's<sup>27</sup> fourth cardinal symptom complex, "nephritis," sufficed. Von Schrotter,<sup>28</sup> in 1899, implicated the "renal, abdominal, neuromuscular, cardiac and bronchial" systems. Harbitz,<sup>29</sup> in 1927, added the "cerebral and cutaneous" systems.

In the present series of 101 cases, diagnosis was made ante mortem in 26, including 2 of our own 6 cases. Most of these diagnoses were made by means of biopsy either of a cutaneous nodule or of a piece of muscle. Surgical specimens and laparotomy also afforded good opportunities for diagnosis. In several instances necropsy served to corroborate the suspected clinical diagnosis.

We believe, with Spiegel,<sup>30</sup> that "the syndrome is not complete without emphasis on the real clinical characteristic—a disproportion between the number and intensity of the symptoms and the disease which is assumed to be their cause." Thus it is in cases in which the diagnoses

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25 Meyer, P. S. Ueber Periarthritis nodosa oder multiple Aneurysmen der mittleren und kleinen Arterien, *Virchows Arch f path Anat* **74** 277, 1878.

26 Brinkmann. Zur Klinik der Periarthritis nodosa, *Munchen med Wchnschr* **69** 703 (May 12) 1922.

27 Christeller, E. Ueber die Localisationen der Periarthritis nodosa, besonders in den Bauchorganen, *Arch f Verdauungskr* **37** 249, 1926.

28 von Schrotter, L. Ueber Periarthritis nodosa, *Wien klin Wchnschr* **12** 404, 1899.

29 Harbitz, F. Different Forms of Arteritis, Especially Periarthritis Nodosa, *Internat Clin* **1** 130 (March) 1927.

30 Spiegel, R. Clinical Aspects of Periarthritis Nodosa, *Arch Int Med* **58** 993 (Dec) 1936.

that are advanced generally seem to be poorly supported and do not satisfactorily explain all the manifestations that the diagnosis of periarteritis nodosa must be most seriously considered

#### PROGNOSIS

Of the 101 patients, 10 were reported as "recovered"<sup>31</sup> at the time the case was described. We have communicated with each author who reported a case with recovery and have received replies from all but one. No follow-up information could be obtained in 3 cases. In the 6 remaining cases, 1 patient had died of what was apparently a coronary lesion, and the other 5 are alive at the time of this writing. Thus, 9 of the 10 patients may still be alive. Although these revised statistics indicate that the former prognosis of "100 per cent fatal" is incorrect, they show that cases in which there is recovery or long survival are exceptional.

#### TREATMENT

Unfortunately, recovery in the reported cases did not follow any known therapy. *S. pallida* has long been discredited as the possible etiologic agent. Nevertheless, each succeeding report on periarteritis nodosa almost invariably has mentioned the 2 cases in the literature in which arsphenamine therapy was employed, that reported by Schottstaedt and that by Carling and Hicks. Neither of the patients had a positive serologic reaction. Despite many statements in the literature to the contrary, Carling and Hicks used arsphenamine merely as a provocative test in attempting to reverse the negative serologic reaction of their patient. This procedure failed, however. We can conclude only that no treatment for periarteritis nodosa, other than symptomatic, can be recommended at present.

#### COMMENT

From the analysis of the data in our charts, as summarized in tables 2 and 3, certain conclusions seem to be justified. Periarteritis nodosa is seen more frequently in males than in females. It occurs chiefly in adult life, but in no special decade. In slightly more than

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31 (a) Carling, E. R., and Hicks, J. A. B. A Case of Periarteritis Nodosa Accidentally Recognized During Life, *Lancet* **1** 1001 (May 19) 1923. (b) Schottstaedt, W. E. R. Periarteritis Nodosa with Remission of Symptoms, *California & West Med* **36** 186 (March) 1932. (c) Motley, L. Periarteritis Nodosa, with Report of Case Showing Unusual Features and Apparent Recovery, *J. A. M. A.* **106** 898 (March 14) 1936. (d) King, E. F. Ocular Involvement in a Case of Periarteritis Nodosa, *Tr. Ophth. Soc. U. Kingdom* **55** 246, 1935. (e) Bernstein, A. Periarteritis Nodosa Without Peripheral Nodules Diagnosed Antemortem, *Am. J. M. Sc.* **190** 317 (Sept.) 1935. (f) Cohen, Kline and Young.<sup>18</sup> (g) Spiegel.<sup>30</sup> (h) Our case 2.

one-half the cases the onset is rapid. The duration of the disease usually is a matter of months, although Macaigne and Nicaud<sup>32</sup> described a case in which the illness lasted for twelve years. The patient in case 2 in our series is now entering his fourth year since the onset of symptoms. In the last two years he has been entirely asymptomatic. An examination just prior to the writing of this report disclosed a recent gain of weight, a normal blood pressure, normal urine and no essential physical deviation from the normal. The absence of abnormal urinary findings at any time offers itself as an explanation for the continued well-being, for we have been struck repeatedly by the sharp downhill course that the patients pursue once renal impairment has set in.

As already noted, our analysis did not yield any truly characteristic or diagnostic symptoms or signs. The most frequent findings—fever, leukocytosis, albuminuria, abdominal pain, edema, loss of weight and hypertension—do not represent a clear diagnostic picture. Bernstein<sup>31c</sup> has called attention to the fluctuations in the blood pressures, but we believe that the rapid rise to high levels, as in our case 3, is of greater importance. Such rapid rises are frequently associated with other signs of renal involvement and, as we have pointed out, are especially significant of a relatively rapid fatal termination. The order of frequency of the other symptoms, signs and abnormal laboratory findings agree in the main with those cited by other observers. The frequency of abdominal pain is noteworthy. It may be associated not only with infarcts involving the various abdominal viscera but also with coronary thrombosis and actual perforations of the viscera. The distress in the upper part of the abdomen usually associated with the chronic passive congestion of heart failure is also not uncommon.

In contrast to the frequency of abdominal pain, thoracic pain is relatively rare. This fact is surprising in the face of the frequency of cardiac involvement noted at necropsy. The type of thoracic pain usually reported was typical of angina pectoris. The literature states that pulmonary involvement is rare. Actually, this statement is exaggerated, for reference to table 2 discloses that, although of the five organs summarized the lung was involved least frequently, it was affected in one fourth of the 87 cases in which autopsy was done. The frequent occurrence of cough and dyspnea therefore is not surprising. However, the frequency of cardiac involvement and heart failure was probably the actual cause of the frequent occurrence of cough and dyspnea in the series. Nevertheless, both appeared less frequently than edema, which usually was of cardiac distribution.

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32 Macaigne, M., and Nicaud, P. *Periarterite noueuse (maladie de Kussmaul) à form chronique*, Bull et mém Soc med d hôp de Paris 54 665 (April 21) 1930.

Eosinophilia and nodules in the skin have long been recognized as of diagnostic aid, but, unfortunately, their frequency is not great. Eosinophilia occurred in but 19 instances and nodules in but 16. These recordings are somewhat higher than those given by Gruber.<sup>12</sup> The replacement of the eosinophilia by a marked shift to the left, with a high percentage of polymorphonuclears, coincident with the occurrence of a complication, usually abdominal, is noteworthy and puzzling to the observer. It should serve to raise the question of periarteritis nodosa. In addition to nodules, many other types of cutaneous lesions have been described, chief among which are purpuric rashes, usually macular in type. Urticarial lesions are encountered infrequently.

Several authors<sup>10</sup> have called attention to the frequent finding of splenomegaly. In our analysis (table 2), we were unable to confirm this either in the antemortem accounts or in the postmortem observations. In fact, the spleen is one of the least involved of the major organs, the actual frequency of involvement being 31 per cent, which is but slightly greater than that of the lung by the vascular process. This fact is somewhat against an infectious bacterial agent as the etiologic factor in the disease. Although the incidence of involvement of the liver was rather high, 71 per cent, icterus was mentioned in but 12 of the 101 cases. The explanation may lie either in the failure of many authors to recognize minor degrees of icterus or in its absence during the time of observation though it may have been present at one time during the course of the illness. It is noteworthy that Pass,<sup>13</sup> in a review of the cases of hepatic infarcts in the literature, found periarteritis nodosa to be the most frequent cause of such lesions. In fact, Arkin<sup>20</sup> has said that hepatic and renal infarcts in the absence of endocarditis should make one think of periarteritis nodosa as the cause.

#### SUMMARY

Six additional cases of proven periarteritis nodosa are reported. In 2 of them diagnosis was made ante mortem.

All the cases of periarteritis nodosa reported in the English literature prior to June 1, 1938—101 cases—were studied and the frequency of symptoms, signs and abnormal laboratory findings tabulated. Totals for these are presented.

The data thus assembled do not afford an answer to the question of causation. They do not substantiate the proposed allergic theory.

Although there were 26 antemortem diagnoses in the 101 case reported, an analysis of the clinical symptoms and signs did not reveal a characteristic clinical pattern.

Dr. G. Darrell Ayer prepared the photomicrographs and assisted in analyzing the necropsy material.

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33 Pass, I. J. Infarction of the Liver, *Am J Path* 11: 503 (May) 1935.

# ROENTGEN DIAGNOSIS OF MURAL THROMBI

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Considerable interest has been aroused in the last few years regarding the roentgen diagnosis of mural thrombi. Yet, in reviewing the literature on this subject, I find that few mural thrombi have been roentgenologically recognized during life and the diagnosis confirmed by necropsy.

From my own experience and that of other observers it is apparent that calcified mural thrombi usually occur in mitral stenosis and are commonly situated in the left auricle. Only 5 cases of mural thrombosis have been reported in the literature. These consist of 3 cases of calcified mural thrombi reported by Scholz,<sup>1</sup> Besser and Schilling<sup>2</sup> and Heeren<sup>3</sup> and 2 cases of noncalcified mural thrombi reported by Arendt<sup>4</sup> and Fussl.<sup>5</sup>

Prompted by this situation, I wish to report a case of calcified mural thrombus in which the condition was recognized during life and the diagnosis confirmed by necropsy.

Roentgenoscopic and aimed roentgenographic technics are important factors in recognizing mural thrombi. One should search for the lesions carefully, with the eyes well adapted under the roentgenoscope and with the smallest diaphragm. Preferably the patient should be placed in the right oblique position. Calcified mural thrombi are round or semilunar. They are rather dense and sharply outlined. Larger than valvular calcifications, they have a dancing motion which is synchronous with the heart beat.

Noncalcified mural thrombi may be recognized by variation in the contour of the normal cardiac silhouette. Lying within the cardiac

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1 Scholz, T. Röntgenologische Darstellung von Herzthromben, *Fortschr a d Geb d Röntgenstrahlen* **32** 416, 1924

2 Besser, P, and Schilling, C. Zur Klinik und Röntgenologie der Herzthromben, *Deutsches Arch f klin Med* **175** 50, 1933

3 Heeren, J. Zur Röntgendiagnose verkalkter Herzthromben, *Fortschr a d Geb d Röntgenstrahlen* **50** 490, 1934

4 Arendt, J. Röntgendiagnose Herzthromben, *Röntgenpraxis* **2** 828, 1930

5 Fussl, E. Beitrag zur Röntgendiagnose, der nichtverkalkten Herzthromben, *Röntgenpraxis* **8** 377, 1936

shadow, the thrombus may be seen as a denser shadow which moves only slightly during systole. Because of its similarity to the cardiac shadow, however, it is seldom recognized. In some cases one can definitely recognize a noncalcified mural thrombus only if it becomes so large that it causes a marked change in the normal cardiac configuration.

#### REPORT OF A CASE

V M, a 56 year old married Italian woman, was admitted to the Bellevue Hospital on Jan 14, 1938, suffering from dyspnea and edema of the ankles. She had been admitted to several hospitals for varying periods because of dyspnea, edema or palpitation, and apparently remaining until improvement occurred, after which she was discharged to continue invalidism at home.

Physical examination revealed an undernourished, emaciated woman who was cyanotic, dyspneic and orthopneic. Malar flush was present, and the temporal veins were dilated. The veins of the neck were distended and pulsating. The lungs revealed moist rales at both bases. The heart was greatly enlarged to right and left, with the point of maximal impulse in the anterior axillary line. There was a systolic thrill at the apex, with a rough systolic blow, a diastolic rumble and a blowing systolic murmur at the base. There was no aortic diastolic murmur. The aortic second sound was faintly heard over the vessels of the neck. The pulmonic second sound was accentuated. There was rapid auricular fibrillation. The liver was large and tender and was located 4 fingerbreadths below the costal margin. There was edema of the sacrum and of the lower extremities up to the mid thigh. During her stay in the hospital the patient received digitalis, ammonium chloride and mercupurin (a mercurin-theophylline preparation), oxygen was administered nasally, and thoracentesis was repeatedly performed on the right. The course was progressively downward, with congestive heart failure. The patient died on May 2.

*Laboratory Data*—The electrocardiogram revealed auricular fibrillation. There was left ventricular preponderance. The T waves in leads I and II were inverted, showing the effect of digitalis. The Wassermann reaction was negative. The hemoglobin content of the blood was 72 per cent. The erythrocyte count was 4,310,000.

*Röntgen Examination*—The thorax was asymmetric, owing to scoliosis of the dorsal part of the spine. The heart was markedly enlarged to the right and left, the right median diameter was 84 cm and the left median diameter 98 cm, the transverse diameter of the heart was 182 cm, the diameter of the chest was 212 cm (fig 1).

The heart was of mitral configuration, the left ventricular arch was intensified and the apex rounded and elevated. The right cardiac border was irregular, with multiple irregular calcifications, which were localized in the lateral view as linear calcified shadows. The posterior and lower cardiac border revealed pleural adhesions to the right side of the diaphragm.

Fluoroscopic examination revealed a calcified semicircular ring just to the left of the midplane, showing a dancing motion toward the apex suggestive of calcification of the mitral valve (fig 2). Another oval calcified ring, which appeared to be smooth, was seen in the posteroanterior position. By rotating the patient in the right oblique position the semicircular, sharply outlined and intensified shadow could not be projected outside the cardiac silhouette and appeared to lie within the left auricle. In the left oblique view the dense, semicircular shadow was at the same level, yet it lay about 0.5 cm from the cardiac border and was clearly

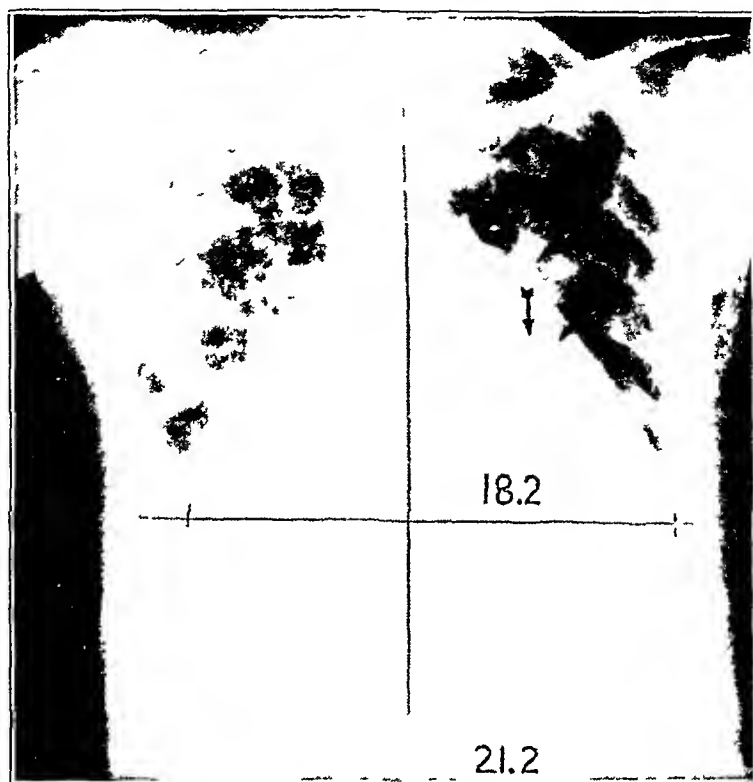


Fig 1—Posteroanterior view of a markedly enlarged heart, with a dense shadow of calcification of the mitral valve



Fig 2—Right anterior oblique view of the heart *A*, calcification of the mitral valve *B*, dense calcification of the left auricle



visible within the cardiac silhouette (fig 3) Beneath these were seen irregular, linear, segmented calcium shadows showing only minimal pulsation When the patient was rotated these were seen running parallel to the cardiac border, suggesting pericardial calcification (fig 4)

*Necropsy*—The heart weighed 450 Gm The pericardium was calcified posteriorly over an area about 7 cm in diameter The heart lay free in the pericardial sac, which contained 200 cc of clear yellowish fluid The epicardium was smooth and of normal transparency The right auricle was dilated to about twice its normal size The fossa ovalis was closed, the endocardium was normal, and the right auricular appendage was free of thrombi The tricuspid ring admitted three fingers The valve cusps showed thickened edges, with no visible verrucae The valve appeared competent, the chordae tendineae were thickened, shortened and



Fig 3—Left oblique view of the heart *A*, semicircular calcification of the mitral valve *B*, dense calcification of the left auricle

fused The papillary muscles were hypertrophied, as were the trabeculae carneae and the myocardium of the dilated right ventricle The muscle wall measured 3 to 10 mm in thickness The endocardium of this chamber was normal The pulmonic valve was normal The pulmonary arteries showed many soft atherosclerotic plaques The left auricle presented a bizarre aspect It was dilated to two or three times the normal size Most of the endocardial surface was covered with adherent, friable, crumbling thrombotic material, which completely filled and distended the auricular appendage This had undergone organization and calcification, so that the appendage projected perpendicularly from the auricle as a bony nodule The cusps of the mitral valve were so thickened and fused that the opening was narrowed to a fish-mouth-like slit of 5 to 10 mm The leaflets were stiff with calcific deposits (fig 5) The chordae tendineae were so shortened



Fig 4—Lateral view of the heart *A*, fish-mouth-like slit of the calcified mitral valve *B*, linear calcified shadow of the left auricle *C*, irregular pericardial calcification running parallel to the cardiac border



Fig 5—Autopsy specimen, with opening into the left auricle *A*, calcified appendage of the left auricle, *B*, mural thrombus of the left auricle, *C*, fish-mouth-like slit of the calcified mitral valve (unopened), *D*, right auricle, *E*, right ventricle, and *F*, aorta

that the cusps were practically attached to the papillary muscles. The greatly thickened and fused chordae could not be clearly differentiated from the thickened edges of the valve cusps. The left ventricle was of normal size, its endocardium and myocardium appeared normal. The latter measured 1 to 1.5 cm in thickness. The aortic ring was normal in size, with no thickening of the valve cusps. The coronary arteries had normal ostiums, showing slight thickening of the walls in places, but no yellowish atheromatous or calcified plaques were present. The aorta was small and elastic, the intima showed a few atheromatous plaques, none of which were calcified or ulcerated.

The spleen weighed 150 Gm. The capsule was not thickened. The parenchyma revealed a firm, fibrous pulp, the malpighian bodies were not discernible. The capsule of the liver was of normal transparency and was smooth except over the diaphragmatic surface, where there were fibrous adhesions. The cut surface revealed a marked distortion of the normal architectural markings and apparent contraction of the lobules, with some replacement by fibrous tissue.

#### COMMENT

This case is of particular interest because it presents three types of intracardiac calcification: mural thrombus of the left auricle, calcification of the mitral valve and pericardial calcification. Although difficult, the differential diagnosis can be made with modern roentgenoscopic and roentgenographic technique.

Calcified valves are situated more medially than calcified coronary arteries. The calcified mitral valves are seen more to the left of the spine in the direct posteroanterior view and near the posterior cardiac wall in the left antero-oblique view. The aortic valves are located low at the left border of the spine in the former view and about in the middle in the latter view. They are usually semilunar, the mitral valve showing a marked pulsatory movement toward the apex and the aortic valve showing a dancing motion.

Calcified mural thrombi usually occur in mitral stenosis and are commonly situated in the left auricle. They are round or semilunar, dense and sharply outlined. They are larger than the valvular calcifications and show a dancing motion.

Calcified cardiac aneurysms appear semilunar and large, with a strong systolic pulsation. Their site of predilection is near the apex. Pericardial calcifications are more frequently located on the lower surface of the right ventricle but also occur in the coronary sulcus, usually leaving the apex free. They are solid, linear and often branching and have only a minimal pulsation. On rotation of the patient they can be seen to run parallel to the cardiac border.

Calcified costal cartilages are denser and more clearcut, and one may identify them by following their course. Calcified glands and calcifications in the lungs and mediastina are round and dense. By rotation of

the patient these can be projected outside the cardiac shadow. They move upward and downward with respiration. The bronchi can be easily differentiated.

#### SUMMARY

A case of calcified mural thrombus of the left auricle is presented with the purpose of demonstrating the great diagnostic value of roentgenoscopic and roentgenographic technic. In this case there were three types of intracardiac calcification: calcification of the mitral valve, pericardial calcification and mural thrombus of the left auricle. These were clearly differentiated *in vivo* and confirmed by necropsy.

As roentgenoscopic and roentgenographic technic improves, an ever growing number of cases of mural thrombus of the left auricle will be recognized. However, the successful roentgenologic diagnosis will be made more frequently than it has been in the past only if one is vigilant and constantly aware of the possible existence of such a lesion.

# Progress in Internal Medicine

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## BLOOD

A REVIEW OF THE RECENT LITERATURE

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RAPHAEL ISAACS, M D

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AND

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The present review includes articles on phases of hematology published in 1938 and a few articles that appeared in 1937 but were not included in the last review. Because of the increasing number of publications it has been necessary to select certain articles, somewhat arbitrarily at times, and some important contributions no doubt have been omitted. These may be included in forthcoming reviews of articles on diseases of the blood. The trend of hematology appears to be toward the increased reference to the state of the bone marrow in various conditions, especially observations derived from material obtained on sternal puncture, the increased use of quantitative data, the establishment of data for "normal" conditions and the chemical physiology and pathology of disease.

### PERNICIOUS ANEMIA

Askanazy<sup>1</sup> has gathered statistics as to the distribution of pernicious anemia in various parts of the world. The incidence varied from no cases in twenty years in Java to 9.1 in Canada and 9.18 per hundred thousand in Sweden. The incidence for the United States is given as 6.9. The percentage shown for autopsy studies varied from 0.04 in Tübingen, Germany, to 1.39 in Warsaw. Data as to various body lengths, weights, state of nourishment and weights of the bone marrow, spleen and liver have been given. The incidence of funicular myelosis varied from 4.7 per cent in a series studied in Munich to 60 per cent in a series studied in Toronto. Data for constitutional hemolytic anemia, constitutional achylic anemia and secondary anemias and leukemias have been given.

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<sup>1</sup> Askanazy, M. Die pathologische Anatomie der Anämien, in *Comptes rendus de la troisième Conférence internationale de pathologie géographique*, Helsingfors, Mercator Tryckeri, 1937, p. 32.

The present status of knowledge relating to nutritional deficiencies and the macrocytic anemias was considered in the Goulstonian Lecture delivered by Ungley<sup>2</sup> before the Royal College of Physicians on March 8, 1938. His own experiments confirmed Meulengracht's observation that the pepsin and the antianemic factor are disassociated physiologically and anatomically in the stomach of the swine. For example, the mucosa of the fundus contains pepsinogen but no intrinsic factor, whereas the mucosa of the pylorus does not contain appreciable amounts of pepsin or pepsinogen but is a good source of the intrinsic factor. In view of these observations, it is interesting to note that Magnus and Ungley<sup>3</sup> observed that the stomachs of 7 patients with pernicious anemia at necropsy showed profound atrophy involving all the coats of the wall and localized to the body of the organ. The pyloric antrum and duodenum, where it had been assumed that the intrinsic factor of Castle was produced, showed no pathologic abnormality. These findings therefore provide an anatomic basis for the achylia gastrica but not for the absence of the intrinsic factor, if it is assumed that it is produced in the regions mentioned. According to these authors, the same unexpected findings were observed by Meulengracht, who transmitted this information to them in a personal communication. From a study of their material, they concluded that the gastric lesion in pernicious anemia is almost certainly not the end result of inflammatory gastritis. It is to be regarded as more of the nature of an atrophic process the cause of which is unknown but which may be the end result of some endocrine or nutritional deficiency or perhaps may even be of congenital origin. They concluded that probably regeneration to normal gastric mucosa never occurs. This statement may be correct, but one wonders if regeneration is any more unlikely in the gastric mucosa than in the papillae of the tongue, where it is known to occur. No data were given to indicate the status of the blood of the patients whose stomachs were examined, and it is not known therefore whether they died in a hematologic relapse or after effective treatment had been given. It is conceivable to us that the gastric mucosa may vary in appearance at different stages of the disease.

Present knowledge concerning the extrinsic factor was summarized by Ungley<sup>2</sup> as follows. Its presence has been confirmed in brewers' yeast, rice polshings, eggs, milk, liver, fraction G of Cohn, liver fractions which are free from protein and polypeptides, and possibly tomatoes. Strauss and Castle postulated (1932) that it might be vitamin B<sub>12</sub>,

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2 Ungley, C. C. Some Deficiencies of Nutrition and Their Relation to Disease. II. Nutritional Deficiency in Relation to Anemia, *Lancet* **1**: 875, 925 and 981, 1938.

3 Magnus, H. A., and Ungley, C. C. The Gastric Lesion in Pernicious Anaemia, *Lancet* **1**: 420, 1938.

but Ungley and James found that this substance was relatively ineffective as a source of the extrinsic factor. It is concluded that vitamin B<sub>6</sub> (the antidermatitic factor in rats) and nicotinic acid are not the extrinsic factor of Castle.

The following data concerning the intrinsic factor of Castle were presented by Ungley. This factor is readily destroyed by heating to 70 or 80 C for one-half hour, it is not identifiable as hydrochloric acid, pepsin, pepsinogen, rennin or lipase. He considers that his work has disproved Greenspon's theory that the gastric factor potent against pernicious anemia is a hormone effective alone if protected from the action of pepsin. His evidence in this respect was the demonstration that depepsinized gastric juice and pepsin-free extracts of pyloric mucosa have no significant hemopoietic effect unless interaction with a source of the extrinsic factor is allowed. It is his belief that the synthesis of a thermostable product identical with the active principle of liver has not yet been accomplished.

In summarizing the knowledge concerning the active principle of liver he stated that a peptide has been obtained which is twice as potent as the original fraction isolated by Dakin and West. Although kidney is as effective as liver, and brain is about one-third as potent, all attempts to isolate potent fractions from these organs have failed. Ungley considers that the antianemic activity of kidney is not due to the presence of the intrinsic factor, because it is retained after heating to 95 to 100 C for two hours.

In considering tropical macrocytic anemia, which responds to the administration of autolyzed yeast, Ungley stated that the observations of Wills indicate that this condition is not usually influenced favorably by purified liver extract (anahaemin). He concluded from this that some mechanism other than a deficiency of Castle's intrinsic factor is involved in the production of this syndrome.

According to Wills and Evans,<sup>4</sup> tropical macrocytic anemia resembles pernicious anemia, as the changes in the blood and the alterations in the bone marrow are similar. The cause of tropical anemia is related to that of pernicious anemia, for in the former it at present is regarded as a deficiency state due to the lack of Castle's extrinsic factor, which results in a deficiency in the body of the liver principle that is curative in pernicious anemia. This view is supported by the observation that tropical anemia responds well to treatment with either liver extract or substances such as autolyzed yeast extract which are known to be good sources of the extrinsic factor. Wills and Stewart, in 1935, observed that anemia which was considered to be the animal counter-

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<sup>4</sup> Wills, L., and Evans, B. D. F. Tropical Macrocytic Anaemia. Its Relation to Pernicious Anemia, *Lancet* 2 416, 1938.

part of tropical anemia could be produced in monkeys by a faulty diet. This anemia responded to autolyzed yeast extract (marmite) by mouth and to liver extracts by oral and parenteral routes. It was found, however, that these animals failed to respond to the more highly purified extracts, even in enormous doses. This led to a study of the action of these refined extracts in tropical anemia in human beings. Clinical trials showed that patients with tropical macrocytic anemia did not respond, as shown by failure of the reticulocytes or red blood cells to increase in number, to the injection of highly purified liver extracts (anahaemin, examen and fractions made from campolon by ammonium sulfate extraction). These preparations are known to be highly potent when given to patients with pernicious anemia. The investigators concluded that this fact further differentiates tropical anemia from pernicious anemia and indicates that there is some new hemopoietic factor present in crude liver preparations and autolyzed yeast products. Judging from their experiments on monkeys, this factor is not vitamin B<sub>1</sub>, vitamin B<sub>4</sub>, riboflavin or nicotinic acid, but it has not yet been separated from the yeast—fuller's earth filtrate of Edgar and McCrae. It is suggested that the missing factor is some part of the vitamin B complex.

It was stated by Wilkinson, Klein and Ashford<sup>5</sup> that in 1934 Wilkinson and Klein were able to prepare by the action *in vitro* of certain fractions obtained from hog's stomach on beef, an active protein-free product which resembled the liver principle and was effective when administered parenterally as well as orally. In their recent investigation they have been able to show that stomachs from patients with pernicious anemia, who have or have not received potent antianemic therapy, do not contain an active fraction which they call haemopoietin and which they consider to be identical with the intrinsic factor. This substance was found to be present in normal stomachs when examined under similar conditions. They believe therefore that their observations demonstrate the presence of the antianemic enzyme hemopoietin in the normal stomach and the deficiency of this substance in the stomachs of both treated and untreated patients with pernicious anemia. These observations are in accordance with their theory, already advanced, that the active antianemic principle of liver is elaborated as the result of an interaction between (1) an unknown substance in beef (the extrinsic factor), and (2) the intrinsic factor (hemopoietin). Wilkinson and Klein consider that they have demonstrated the occurrence of this reaction *in vitro* and also that it takes place *in vivo* in the normal stomach but not in the stomach of the patient with pernicious anemia.

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5 Wilkinson, J. F., Klein, L., and Ashford, C. A. The Hematopoietic Activity of the Human Stomach in Pernicious Anemia, *Quart. J. Med.* 7:555, 1938.



Morrison<sup>6</sup> reported that patients with pernicious anemia treated with orally administered depepsinized gastric mucosa, prepared by Greenspon's process, showed almost completely negative results. In this observer's opinion the process of depepsinization inactivates the anti-anemic activity of the gastric mucosa by destroying the intrinsic factor. He concluded further that the role of pepsin in pernicious anemia is not clear and that his investigation has proved only that the process of depepsinization is responsible for the destruction of antianemic activity of the preparations.

As previously stated Klein and Wilkinson,<sup>5</sup> in 1933 and 1934, isolated from hog's stomach concentrated fractions which contained the antianemic factor. Furthermore, when these fractions were incubated with beef, "a relatively thermostable and therapeutically effective concentrate could be made from the products of digestion." Klein and Wilkinson ascribed an enzymic nature to the substance which they call haemopoietin and which they consider to be "identical" with Castle's hypothetic enzyme of gastric juice. They implied that the absence of this substance from the stomach is an important etiologic factor in pernicious anemia. They concluded from their own experiments and those of others that "the site of action of haemopoietin is in the neutral or more alkaline regions of the gastro-intestinal tract rather than in the more acid regions of the stomach."

The experiments of Jones, Grieve and Wilkinson<sup>7</sup> were designed to study further the enzymic properties of fractions of hog's stomach. To accomplish this the interaction of fractions of hog's stomach with myoglobulin from beef and with caseinogen was studied, and the results were compared with those obtained when pepsin was used. The effect of the preparations of hog's stomach was similar to that of pepsin, but there are several interpretations of this observation. Abundant proof exists that hemopoietin and pepsin are not identical, and contamination of the former with the latter must be considered when explaining the similarity of the properties of the two enzymes. A third possibility is that hemopoietin differs from pepsin but has similar properties.

Taylor, Castle, Heinle and Adams<sup>8</sup> have made observations which indicate a similarity between the proteolytic activity of normal human

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6 Morrison, S. A Comparison of Anti-Pernicious Anemia Potency of Depepsinized and Undepepsinized Gastric Mucosa, *J Lab & Clin Med* **23** 949, 1938.

7 Jones, T S G, Grieve, W S M, and Wilkinson, J F. Investigations on the Nature of Haemopoietin, the Anti-Anaemic Principle in Hog's Stomach. The Interaction of Haemopoietin and Pepsin with Myoglobulin and Caseinogen, *Biochem J* **32** 665, 1938.

8 Taylor, F H L, Castle, W B, Heinle, R W, and Adams, M A. Observations on the Etiologic Relationship of Achylia Gastrica to Pernicious Anemia. Resemblances Between Proteolytic Activity of Normal Human Gastric Juice on Casein in Neutral Solution and Activity of Intrinsic Factor, *J Clin Investigation* **17** 335, 1938.

gastric juice on casein in neutral solution and the activity of the intrinsic factor. They have observed that incubation of gastric juice and a casein solution at 37.5 C and a  $p_H$  of 7.4 results in a progressive increase in the nitrogenous substances in the trichloroacetic filtrates of these digests. Furthermore, the activity of both the gastric secretions and the intrinsic factor is not dependent on the presence of saliva or regurgitated duodenal contents, both types of activity are absent or greatly diminished in the gastric secretion of patients with Addisonian pernicious anemia, they are not destroyed by Berkefeld filtration or exposure to alkali, they are both destroyed by exposure to 40 C for seventy-two hours and to 70 to 80 C for thirty minutes or by baking for five minutes and are inhibited by an acidity greater than  $p_H$  3.5. The *in vitro* activity of normal human gastric juice is entirely eliminated by contact with Lloyd's reagent (specially prepared siliceous earth), whereas others have stated that this substance removes only a portion of the intrinsic factor. This study indicates, as one might anticipate, that the proteolytic activity of gastric juice and the activity of the intrinsic factor are influenced by similar alterations in their environment. As they are both produced by the stomach, it seems logical to assume, in our opinion, that they would be susceptible to the same physical and chemical influences.

Bachrach and Fogelson,<sup>9</sup> after a careful review of the literature, came to the conclusion, with which we are in accord, that no normal laboratory animal has yet been found which exhibits a sufficiently uniform or characteristic reaction to antianemic substances to permit its use for assay purposes. For a period of two years they observed 7 dogs from which 30 cm of jejunum, the duodenum and the distal seven-eighths of the stomach had been removed. The experimental animals recovered rapidly from the operation and within a few months were indistinguishable from normal animals. At no time did any of the 7 animals show a blood picture even suggestive of pernicious anemia, although they all had transient "secondary anemia," from which all but 1 recovered. Although these investigators failed to accomplish their purpose, nevertheless their results are of great theoretic importance. As they pointed out, the changes in the blood should have succeeded if Meulengracht's hypothesis had been applicable to the dog. Their results show clearly that it is not, for he submitted evidence which indicated that the intrinsic factor of Castle has its source chiefly in the pyloric glands of the stomach and the glands of Brunner in the small intestine. The observations of Fogelson and Bachrach indicated that if the source of the intrinsic factor in the dog is the "pyloric gland organ," other parts of the body must participate in this function.

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9 Bachrach, W. H., and Fogelson, S. J. The Role of the Upper Gastrointestinal Tract in the Etiology of Pernicious Anemia. *J. Lab. & Clin. Med.* 24: 249, 1938.

Potent liver extract was examined by Jacobs<sup>10</sup> for the presence of choline, because he had previously reported that a reticulocyte response had been observed following the oral administration of potato juice and tyrosine. For this reason he thought it justifiable to examine liver extract to determine whether or not some of the simpler nitrogenous bases, such as choline, were present, as they are known to occur in potatoes and other plants. It was determined that at least 1 per cent of choline was present in one preparation of liver extract for oral administration,<sup>11</sup> and studies are contemplated to investigate the rather remote possibility of its effect on pernicious anemia.

Jequier and Apsey<sup>12</sup> consider that there was evidence which suggested that as the antianemic principle was widely diffused throughout the body and in the kidney, it should be eliminated in the urine, like so many hormones. If this could be established, it would be of interest, first, in indicating that the metabolism of the principle is not confined to the alimentary tract and liver, and, second, it would be of possible diagnostic importance, for the principle might be absent from the urine of patients with pernicious anemia. It was determined that the urine of untreated patients with pernicious anemia, as well as normal urine, contained a substance which when injected subcutaneously provoked a reticulocyte response in the white rat. In our opinion, however, the accuracy of this conclusion may be challenged, as the reticulocyte counts were recorded for only three to five days after the injection, and the maximum increase shown was 40 per cent. One patient with pernicious anemia, whose red blood cell count was 1,820,000 per cubic millimeter, was given a drop by drop rectal infusion of 300 to 500 cc. of normal urine, which was repeated twice. This was not followed by an increase in the reticulocyte count or evidence of subjective improvement. The patient subsequently responded satisfactorily to the injection of potent liver extract. They concluded that human urine contains a substance capable of producing a reticulocyte response in the white rat. Normal urine, however, showed no therapeutic activity in 1 case of pernicious anemia.

Schiff, Rich and Simon<sup>13</sup> studied the hemopoietic effect of injections of extracts prepared from the livers of 3 patients with cirrhosis of the liver who had macrocytic anemia. Two of them had hepatic cirrhosis,

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10 Jacobs, H. R. On the Nature of the Antipernicious Anemia Principle. Search for Nitrogenous Bases. Isolation of Choline, *J. Lab. & Clin. Med.* **24** 128, 1938.

11 The liver extract used was that prepared by Eli Lilly & Co.

12 Jequier, E., and Apsey, G. R. M. Anti-Pernicious Anemia Principle. Some Experiments with Urine, *Brit. M. J.* **2** 934, 1938.

13 Schiff, L., Rich, M. L., and Simon, S. D. The "Hematopoietic Principle" in the Diseased Human Liver, *Am. J. M. Sc.* **196** 313, 1938.

and the third had carcinoma of the hepatic duct with cirrhosis and hepatic metastases. Each patient had definite macrocytic anemia, 1 had received treatment with a commercial liver extract preparation a month before death, without effect, the second patient "had at no time during his illness received antianemic therapy other than iron," no statement was made about antianemic therapy in the third case. When liver extract was made from the diseased livers of these 3 patients and given intramuscularly to untreated patients with pernicious anemia, characteristic reticulocytosis and an increase in the hemoglobin value and red blood cell count resulted. It was concluded from these experiments that human liver may contain the specific hemopoietic principle even when extensively diseased and that this statement holds true even when a patient with diseased liver has associated macrocytic anemia. Naturally, these experiments suggested that the macrocytic anemia associated with hepatic disease is not caused by failure of the liver to store the specific antianemic substance. Their results are at variance with those reported by Goldhamer, Isaacs and Sturgis in 1934, who observed that an extract prepared post mortem from the liver of a patient with cirrhosis and macrocytic anemia was ineffective in eliciting a hemopoietic response when administered parenterally to a patient with pernicious anemia in relapse. The studies by Schiff and his collaborators suggested strongly that macrocytic anemia in a patient with cirrhosis of the liver must, in some instances, be due to causes other than an inability of the liver to store the hemopoietic principle, but they did not offer an explanation of this. The fact that an extensively diseased liver which contains the active principle may be present in a patient with macrocytic anemia was noted by Goldhamer and his associates in their original publication.

Pernicious anemia is now believed to be caused by simple deficiency of a substance which is required specifically for the maturation of erythropoietic cells, but previously it was commonly supposed to be a hemolytic anemia. In order to clarify the nature of the mechanism of this anemia, the rate of excretion of coproporphyrin I as an index of the activity of the bone marrow and, concurrently, the quantitative measurements of urobilin excretion have been made by Dobriner and Rhoads<sup>14</sup> to estimate the rate of blood destruction. By studying the coproporphyrin I and urobilin excretion of patients with pernicious anemia in relapse and during therapeutically induced remissions, they reached the following conclusions: 1. During relapse, erythrocytes are being formed and also destroyed more rapidly. 2. During a remission the rate of destruction returns quickly to normal, and at the same time the rate of formation becomes less. These observations are interpreted

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<sup>14</sup> Dobriner, K., and Rhoads, C. P. Metabolism of Blood Pigments in Pernicious Anemia, *J. Clin. Investigation* **17** 95, 1938.

to indicate that hemolysis is a factor in pernicious anemia. The authors do not regard this concept as incompatible with the etiologic mechanism described by Castle, as they stated that "it suggests only that the Castle mechanism should include hemolysis operative only in the presence of a deficiency."

Rhoads and Miller<sup>15</sup> observed that the combination of aminopyrine and a diet producing black tongue caused anemia in dogs. This suggested that indole, as a representative of the aromatic compounds, produced by endogenous metabolism, might have a similar action on the blood. It is believed that indole is converted into indican by the liver and excreted by the kidneys, as indicated by its presence in the urine and its accumulation in the blood after the removal of both kidneys. Anemia in mice has been observed after the injection of indole. Also, indicanuria and anemia which is amenable to liver extract therapy have been produced in dogs which have had surgically formed, inactive, open jejunal segments. Rhoads and Miller observed that the feeding of indole to dogs ingesting a normal diet results occasionally in mild anemia. The combination of indole and a diet producing black tongue causes an anemia which can be cured by adding liver extract orally or by substituting a normal intake of food for the deficient one. Neither indole alone nor an abnormal diet produces marked anemia in experimental animals.

Additional studies were made by these authors<sup>16</sup> to determine the mechanism of production of anemia caused by the effect of indole and a deficient diet. They concluded that the hemolysis caused by indole is enhanced by a deficient diet, that the hemolytic effect can be abolished by supplementing the deficient diet with potent antianemic liver extract, that hemolysis affects all the types of red blood cells, including reticulocytes, and that recovery from the anemia is associated with cessation of the hemolytic process. Although the hemolytic process is an active one in the causation of the anemia, the authors also stated that "an abnormally low rate of production of erythrocytes may well be a factor in the production of the anemia."

Ponder and Rhoads<sup>17</sup> found that with saponin, sodium taurocholate at a  $p_H$  of 7.0, or sodium glycocholate at a  $p_H$  of 6.0, the red blood cells from a patient with pernicious anemia were more vulnerable in vitro than normal cells. During the development of a remission the resistance of the cells returned slowly to normal.

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15 Rhoads, C. P., and Miller, D. K. Induced Susceptibility of Blood to Indol, *J. Exper. Med.* **67** 273, 1938.

16 Rhoads, C. P., Barker, W. H., and Miller, D. K. Increased Susceptibility to Hemolysis by Indol in Dogs Fed Deficient Diets, *J. Exper. Med.* **67** 299, 1938.

17 Ponder, E., and Rhoads, C. P. Red Cell Resistance to Lysins in Pernicious Anemia, *Proc. Soc. Exper. Biol. & Med.* **38** 540, 1938.

Kirk<sup>18</sup> noted abnormally low total phosphatide values in the plasma of patients with pernicious anemia in relapse. After liver therapy for two to four weeks, this value increased, as well as the concentration of ether-insoluble phosphatide of the plasma, and the cerebrosides of the corpuscles. No characteristic differences marked the patients with involvement of the spinal cord.

De Lucia and Russo<sup>19</sup> observed a diminution in the total acid-soluble and lipid phosphorus in all forms of anemia. The inorganic phosphorus was the most variable of the group. In cases of pernicious anemia in which liver preparations were given, there was a definite increase in the total and acid-soluble phosphorus, while the lipid fraction increased slowly.

Mansfeld and Sos<sup>20</sup> found that liver extract would cause regeneration of the blood in rabbits made anemic by repeated injections of small amounts of saponin, only if the thyroid gland was present. After thyroidectomy the response could not be obtained unless a protein-free extract of hydrolyzed thyroid gland was injected. This substance, independent of thyroxin, was designated as the myelotropic hormone of the thyroid. Thyroidectomy did not interfere with the activity of stomach extract.

Groen<sup>21</sup> found diminished absorption of dextrose in 3 patients with pernicious anemia during relapse. The absorption returned to normal after treatment.

Schneiderbauer<sup>22</sup> described 3 cases of chronic deforming polyarthritis in which pernicious anemia developed. The author attributed the pernicious anemia to infectious chronic gastritis, which was considered to be an extension or a part of the infectious process involving the joints.

From observations on 38 patients with pernicious anemia, van der Scheer and Koek<sup>23</sup> concluded that polyneuritis, with corresponding symptoms, was present in some cases. Histologic studies confirmed the view that in pernicious anemia lesions of the peripheral nerves may occur, as well as those of the central nervous system.

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18 Kirk, E. The Concentration of the Individual Phosphatides (Ether-Insoluble Phosphatide, Lecithin and Kephalin) and of Cerebrosides in Plasma and Red Blood Cells in Normal Individuals, and in Pernicious Anemia, *Acta med Scandinav*, 1938, supp, 89, p. 198.

19 de Lucia, P., and Russo, P. Il quadro del fosforo ematico nell'anemia, *Boll Soc ital di biol sper* **13** 701, 1938.

20 Mansfeld, G., and Sos, J. Ueber die Beziehungen der Schilddrüse zur perniziösen Anämie, *Klin Wchnschr* **17** 386, 1938.

21 Groen, J. Absorption of Glucose from the Small Intestine in Deficiency Disease, *New England, J Med* **218** 247, 1938.

22 Schneiderbauer, A. Perniziose Anämie im Verlaufe von chronischer Polyarthritis, *Ztschr f klin Med* **134** 113, 1938.

23 van der Scheer, W. M. and Koek, H. C. Peripheral Nerve Lesions in Cases of Pernicious Anemia, *Acta psychiat et neurol* **13** 61, 1938.

Haring<sup>24</sup> studied polyps of the gastric mucosa in pernicious anemia. Histologically they resemble adenomas of the thyroid gland which occur in cases of exophthalmic goiter or myxedema, and the author suggested that they may be related to incretory activity. A relation between gastric polyposis and pernicious anemia was postulated, and the presence of gastric polyps should lead to study of the patient for possible hyperchromic anemia.

Luhr and Gulzow<sup>25</sup> made gastroscopic studies of patients with pernicious anemia and noted atrophic processes and acute and chronic gastritic lesions. The authors believe that gastritis plays an important part in the pathogenesis of pernicious anemia and that this accounts for the increased protein content of the gastric juice of these patients.

Wintrobe<sup>26</sup> and his collaborators observed young pigs which were fed a diet which was adequate in all respects. As the animals developed, the amount of yeast which was fed was gradually reduced, and thiamin (vitamin B<sub>1</sub>) and riboflavin were substituted for it. Ataxia and loss of reflexes resulted but the motor power of the muscles remained intact. These changes suggested the presence of a sensory defect, which was substantiated at necropsy. There was selective degeneration of the peripheral sensory neuron, involving its cell body in the posterior root ganglion and the peripheral axon. The central axon which was included in the posterior roots and in the posterior columns was likewise affected. There were no clearcut abnormalities in the anterior roots or anterior horn cells. It was thought that these changes were due to a deficiency of one or more components of the vitamin B complex. In further experiments, which are now in progress, the significance of riboflavin, nicotinic acid, vitamin B<sub>6</sub> and other components of the vitamin B<sub>2</sub> complex is being studied. The relation of the neurologic changes observed to those occurring in pernicious anemia and pellagra is a matter only for speculation. The peripheral neuritis and changes in the posterior columns without glial reaction were similar to those seen in subacute combined degeneration of the cord, but in no instance were any changes observed in the lateral columns. The authors properly emphasized, however, that in human beings nutritional deficiencies are usually multiple in character and are therefore not entirely comparable to the experimental dietary defects to which the experimental animals were subjected.

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24 Haring, W. Gutartige Magengeschwulste bei perniziöser Anämie, *München med Wchnschr* **85** 1544, 1938.

25 Luhr, K., and Gulzow, M. Gastritisbefunde bei der Achylia perniciosa. *Gastroskopische Untersuchungen*, *Deutsches Arch f klin Med* **182** 327, 1938.

26 Wintrobe, M. M., Mitchell, D. M., and Kolb, L. C. Sensory Neuron Degeneration in Vitamin Deficiency. Degeneration of Posterior Columns of Spinal Cord, Peripheral Nerves, and Dorsal Root Ganglion Cells in Young Pigs Fed Diet Containing Thiamin (B<sub>1</sub>) and Riboflavin But Otherwise Deficient in Vitamin B Complex, *J Exper Med* **68** 207, 1938.

Suh and Merritt<sup>27</sup> stated that the classic triad of pernicious anemia is hyperchromic anemia, degenerative changes in the spinal cord and defective gastric secretion. They suggested that the changes in the spinal cord may be related to some unknown factor which is independent of the changes in the blood and the achylia gastrica. This may be a defect in absorption of vitamin B, as "suggested by the fact that most of the reported cases have been associated with the conditions which might be accompanied by such a defect." Eight cases of subacute combined degeneration of the spinal cord without macrocytic anemia are reported. The common causes of changes in the posterior and lateral tracts of the spinal cord which produce changes closely resembling those of subacute combined degeneration of the cord, as seen in pernicious anemia, are multiple sclerosis, syphilitic meningomyelitis, syringomyelia and tumors of the spinal cord. These conditions, as well as pernicious anemia, were excluded as far as possible in their reported cases. Three of their patients presented the typical neurologic syndrome associated with pernicious anemia, but there was no significant disturbance of the blood or achylia gastrica. In 1 patient there was outstanding evidence of involvement of both posterior and lateral tracts of the spinal cord. In 3 additional patients there was conclusive evidence of subacute combined degeneration, but in each case there was normal gastric acidity and the anemia was hypochromic in type. In 1 patient there were mild hypochromic anemia, achylia gastrica and evidence of endocrine dysfunction (the syndrome of adiposa dolorosa). The complicating factors were arteriosclerosis in 3 cases, Hodgkin's disease in 1, ulcerative colitis in 1 and glandular dysfunction (adiposa dolorosa) in 1. These observers postulated that an impaired utilization of vitamin B is the most plausible explanation of the symptoms referable to the spinal cord in cases of pernicious anemia. The same factor is the most probable cause of the symptoms and signs of the 8 patients who were observed. It is suggested that this type of disease of the spinal cord is only symptomatic of various disease conditions.

*Therapy*—Von Bonsdorff<sup>28</sup> found that powdered *Bothriocephalus latus* inactivated liver extract, and a similar action in the gastrointestinal tract was postulated. Totterman<sup>29</sup> found that on feeding the powder to

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27 Suh, T, and Merritt, H. H. Combined System Disease Without Obvious Evidence of Pernicious (Macrocytic) Anemia. Report of Eight Cases, One Autopsy, *Am J M Sc* **196** 57, 1938.

28 von Bonsdorff, B. Wird der antianämische Faktor in Leberpräparaten vom *Bothriocephalus latus* zerstört? *Acta med Scandinav* **89** 153, 1938.

29 Totterman, G. Experimental Researches upon the Role of *Bothriocephalus latus* in the Pathogenesis of Pernicious Anemia, *Acta med Scandinav*, 1938, supp 89, p 150, Ueber die Pathogenese der Wurmanämie, *ibid* **96** 268, 1938.



patients with anemia due to *Bothriocephalus* a more severe anemia, with a high color index, developed in 5 of 8 patients. On discontinuance of the use of the powder, the patients recovered. This anemia was not produced in normal persons or in patients with pernicious anemia who were receiving liver or stomach treatment.

Emile Weil<sup>30</sup> has formulated what he characterizes as *le terrain morbide* in pernicious anemia and in aplastic states of the marrow. These include certain hereditary and familial characteristics, gastrointestinal abnormalities, with achlorhydria and achylia, and a certain susceptibility on the part of the bone marrow. In the presence of the proper "soil," certain external factors influence the development of the anemia.

Hanssen<sup>31</sup> commented on the fact that pernicious anemia is not frequent in Norway. It is rare in the three northern counties. In the north and west the rate is 2 per hundred thousand population, while in the east and south it is 4 to 6 per hundred thousand. The death rate for all ages has fallen since 1927, except for patients over 70 years of age, who have shown an increase in rate.

Standards for increases in the red blood cell count after intramuscular liver therapy and after stomach therapy in pernicious anemia were calculated by Isaacs, Bethell, Riddle and Friedman<sup>32</sup>. From the graphs it is possible to determine a standard response expected at weekly intervals. Under ideal conditions a normal red blood cell count is reached in eight weeks with intramuscular therapy.

Standards for the maximum reticulocyte percentage after liver therapy intramuscularly in cases of pernicious anemia were published by Isaacs and Friedman<sup>33</sup>. It was found that the maximum reticulocyte percentage could be expressed by the formula  $\frac{82 - 22 E_0}{1 + 0.5 E_0}$  ( $E_0$  equaling the initial red blood cell count in millions per cubic millimeter).

Mills and Mawson<sup>34</sup> noted that the blood content of bilirubin (van den Bergh reaction) was increased in pernicious anemia during relapse but was lowered after therapy. The average concentration in 85 cases was  $0.98 \pm 0.06$  mg per hundred cubic centimeters. Ninety-three per

30 Weil, P. E. *Le terrain morbide dans le Biermer et les états d'aplasie médullaire*, in *Comptes rendus de la troisième Conférence internationale de pathologie géographique*, Helsingfors, Mercator Tryckeri, 1937, p. 193.

31 Hanssen, O. *The Decrease in Mortality from Pernicious Anaemia in Norway*, *Acta med Scandinav*, 1938, supp. 90, p. 436.

32 Isaacs, R., Bethell, F. H., Riddle, M. C., and Friedman, A. *Standards for Red Blood Cell Increase After Liver and Stomach Therapy in Pernicious Anemia*, *J. A. M. A.* **111**: 2291 (Dec. 17) 1938.

33 Isaacs, R., and Friedman, A. *Standards for Maximum Reticulocyte Percentage After Intramuscular Liver Therapy in Pernicious Anemia*, *Am. J. M. Sc.* **196**: 718, 1938.

34 Mills, J., and Mawson, C. A. *Significance of the van den Bergh Reaction in the Diagnosis of Pernicious Anemia*, *Lancet* **2**: 1455, 1938.

cent of the values were greater than 0.4 mg, whereas 91 per cent of a normal control group had values less than 0.4 mg (average of  $0.1 \pm 0.02$  mg)

Fouts and Helmer<sup>35</sup> found a marked increase in the urea clearance of patients with pernicious anemia after a remission induced with liver extract. Patients with complications accompanied by a low value for urea clearance required a larger dose of liver extract to maintain a normal red blood cell count.

Castellani<sup>36</sup> compared the symptoms of sprue and pernicious anemia. The rhamnose test gave a negative reaction in the former and a positive reaction in the latter.

From a study of forty-five specimens of bone marrow taken from patients with various stages of pernicious anemia, Jones<sup>37</sup> concluded that the megaloblast series of cells form a separate group and die off during liver therapy, being replaced by cells of the normoblast series.

Vesa<sup>38</sup> studied the heart in pernicious anemia. Numerous circulatory disturbances were noted, but only slight changes were apparent in the electrocardiogram. The heart was often enlarged but without a mitral configuration. A murmur was common. Because of the advanced ages of some of the patients, the etiologic relation of the changes was uncertain. After exertion the electrocardiogram showed some changes suggestive of coronary insufficiency, but they were less marked than in coronary stenosis.

Kampmeier and Jones<sup>39</sup> noted that visual symptoms due to atrophy of the optic nerve may be the presenting symptom or an important symptom in pernicious anemia. The symptoms in 3 cases demonstrated the necessity of ruling out the possibility of tabes dorsalis.

Goldstein<sup>40</sup> has summarized the history of the developments of liver therapy in pernicious anemia, tracing it back to 1552.

Okada, Shamoto and Yamase<sup>41</sup> found a substance in spinach which exerted a limited hemopoietic action in a patient with pernicious anemia. They suggested spinach therapy as an adjuvant to liver or stomach treatment.

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35 Fouts, P. J., and Helmer, O. M. Urea Clearance in Pernicious Anemia, *Arch Int Med* **61** 87 (Jan.) 1938.

36 Castellani, A. Sprue and Pernicious Anemia, *Rev Gastroenterol* **5** 226, 1938.

37 Jones, O. P. Nature of the Reticulocytosis in Pernicious Anemia Following Liver Therapy, *Proc Soc Exper Biol & Med* **38** 222, 1938.

38 Vesa, A. Herzsymptome bei Anämien, *Acta med Scandinav*, 1938, supp 89, p 182.

39 Kampmeier, R. H., and Jones, E. Optic Atrophy in Pernicious Anemia, *Am J M Sc* **195** 633, 1938.

40 Goldstein, H. I. Liver Therapy in Anemia, *M World* **56** 244, 1938.

41 Okada, S., Shamoto, M., and Yamase, F. New Therapy in Pernicious Anemia, *Nagoya J M Sc* **11** 147, 1937.

Krantz <sup>42</sup> noted the development of marked allergic phenomena in a patient with pernicious anemia who was treated with liver extract intramuscularly. The patient originally had not shown the expected hemopoietic response when treated orally. Small but increasing amounts of liver extract given intramuscularly eliminated the reactions. Gardner <sup>43</sup> described a similar condition in which the patient was sensitive to liver products taken orally. In Criepe's <sup>44</sup> case the patient acquired sensitivity to liver extract but later was able to tolerate it. Positive cutaneous reactions and reagins were present for at least three months after the initial reaction.

Massobrio and Maranzana <sup>45</sup> made additional studies on the eosinophilia developing in normal persons and in patients with pernicious anemia after liver therapy. It appeared when the liver was raw or almost raw but not when it was thoroughly cooked or when an extract was injected. Schemm <sup>46</sup> has outlined the practical details in the management of pernicious anemia. The average cost of medication is about \$10 per year. The total cost to the patient varies from \$110 to \$170 per year when the intramuscular method of treatment is employed. Case histories of 4 brothers with pernicious anemia were cited. Sturgis, <sup>47</sup> from observations on 1,000 patients with pernicious anemia, outlined seven points in the diagnosis of the disease: (a) achlorhydria, (b) macrocytosis, (c) a high color index, (d) the response to therapy, (e) paresthesia, (f) glossitis and (g) leukopenia or the absence of leukocytosis. The most satisfactory method of treatment is by the intramuscular administration of liver extract. Hansen-Pruss <sup>48</sup> was unable to produce a remission in pernicious anemia, hypochromic anemia, myeloid anemia, idiopathic hypochromic anemia or hypochromic anemia in hepatic disease with the intramuscular or intravenous injection of nicotinic acid in doses of 60 mg per day. After treatment a fall in the white blood cell count of the marrow was noted.

The hemopoietic principle of liver extract is not precipitated by calcium carbonate ( $\text{CaCl}_2 + \text{Na}_2\text{CO}_3$ ) but is absorbed by norite char-

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42 Krantz, C. I. Anaphylactic Reactions Following Medication with Parenteral Liver Extract, *J. A. M. A.* **110** 802 (March 12) 1938.

43 Gardner, J. W. Allergy to Oral Administration of Liver Concentrate, *J. A. M. A.* **110** 2003 (June 11) 1938.

44 Criepe, L. H. Allergy to Liver Extract, *J. A. M. A.* **110** 507 (Feb. 12) 1938.

45 Massobrio, E., and Maranzana, P. L'eosinofilia da ingestione di fegato, *Ricerche cliniche e sperimentali, Arch. per le sc. med.* **65** 201, 1938.

46 Schemm, F. R. The Management of Pernicious Anemia in Private Practice, *Journal-Lancet* **58** 63, 1938.

47 Sturgis, C. C. Remarks on the Differential Diagnosis and Treatment of Pernicious Anemia, *Bull. New York Acad. Med.* **14** 715, 1938.

48 Hansen-Pruss, O. C. Failure of Nicotinic Acid in the Treatment of Anemia, *New England J. Med.* **218** 1050, 1938.

coal Sladek and Kyer<sup>49</sup> found that this extract contains tyrosine There was 0.41 to 0.91 per cent nitrogen Jacobs<sup>10</sup> found that liver extract contains 1 per cent choline

Karrer, Frei and Ringier<sup>50</sup> found that extraction of phosphorus, pentose and most of the purine content did not reduce the hemopoietic activity of liver extract The active material did not contain flavin, pterine, reducing carbohydrate, polypeptides, aminoacetic acid, phenylalanine, tyrosine, histidine or oxyprolin Analysis of an active fraction showed carbon, 45.68 per cent, hydrogen, 6.75 per cent, nitrogen, 14.5 per cent, and some sulfur Mazza and Penati<sup>51</sup> found that neither nucleic acid nor xanthopterin was therapeutically effective in 3 cases of pernicious anemia The urine contained a normal amount of pterine

*Neurologic and Cerebral Manifestations in Pernicious Anemia—*

The frequent occurrence of manifestations in the central nervous system in pernicious anemia has led to the acceptance of the axiom that if neurologic complications are absent in a case of macrocytic anemia, although pernicious anemia is a possibility, other causes should be immediately investigated In the series of 69 patients reported on by Kampmeier and Jones,<sup>39</sup> 75 per cent showed involvement of the central nervous system These figures were well within the range that had been reported previously The cause of the changes in the nervous system remains in the realm of theory Robinson<sup>52</sup> considers that pernicious anemia is a third psychogenic disease and has suggested that it is due to a degenerative lesion of the brain The neurologic manifestations are considered by Suh and Merritt<sup>27</sup> to be the result of vitamin B deficiency Drake<sup>53</sup> carefully studied a patient with pernicious anemia who showed subacute combined degeneration of the spinal cord and concluded from his results that this complication is directly related to the anemia This observation is directly opposed to the findings of Suh and Merritt, who reported a series of cases of combined system disease without obvious evidence of pernicious (macrocytic) anemia That the blood supply (anemia) may have some influence on the function of the central nervous system gains support from the experiments of Bar-

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49 Sladek, J, and Kyer, J Preparation and Properties of the Charcoal Adsorbate of Liver Extract, *Proc Soc Exper Biol & Med* **39** 227, 1938

50 Karrer, P, Frei, P, and Ringier, B H Bestandteile von gegen perniziose Anämie hoch aktiven Leberpräparaten II, *Helvet chim acta* **21** 314, 1938

51 Mazza, F P, and Penati, F Sulla natura chimica del principio anti-pernicioso del fegato, *Arch di sc biol* **24**:83, 1938

52 Robinson, S C Exophthalmic Goitre and Gastroduodenal Ulcer—Two Constitutionally Different Diseases, with a Note on Pernicious Anemia, *Illinois M J* **73** 210, 1938

53 Drake, E H Pernicious Anemia with Subacute Combined Lateral Sclerosis, *Maine M J* **29** 110, 1938

geton<sup>54</sup> This investigator demonstrated that the transmission of impulses through a sympathetic ganglion could be influenced by varying the blood supply A specific neurotoxin due to a disturbance in lipid metabolism has also been considered the causative factor of the pathologic changes in the cord

The most common neurologic symptoms are numbness and tingling of the extremities, coldness, burning, ataxia, loss of finer coordination of the fingers and disturbances of the bowel and bladder Careful studies of the function of the bladder and the need of treatment for this complication have been emphasized by Kickham and Moloney<sup>55</sup> These authors stated that the course may be accurately ascertained by cystometric observations Van der Scheer and Koek<sup>23</sup> have observed 38 patients with pernicious anemia, and it is their opinion that the symptoms frequently noted are due to changes in the peripheral nerves rather than to alterations in the cord In biopsy and autopsy specimens they have demonstrated myelin degeneration, which occurs usually at the periphery and tends to diminish in severity proximally Yang and Chang,<sup>56</sup> who reported the occurrence of pernicious anemia in a Chinese, also concluded from their work that the neurologic manifestations may be due to pathologic changes in the peripheral nerves

The signs are dependent on the site of the lesion (peripheral or central) and the extent of the pathologic involvement The degeneration in the spinal cord may be in the anterior, lateral or posterior columns These tracts may be involved alone or simultaneously As a result, the reflexes may be intensified, decreased or absent No specific mental picture has been observed in pernicious anemia, although cerebral involvement is common Many investigators are of the opinion that the mental manifestations are independent of the disease process of pernicious anemia Romano and Evans<sup>57</sup> cited a case of secondary anemia associated with a psychosis The mental symptoms improved with the elimination of the anemia These authors believe that this same process occurs in pernicious anemia Rotter and Peña Chavarría<sup>58</sup> have studied the influence of tropical anemias on the physiopathologic state of the brain It is their opinion that the anemia, nutritional dis-

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54 Bargeton, D Some Effects of Acute Anemia on the Transmission of Impulses Through a Sympathetic Ganglion, *Am J Physiol* **121** 261, 1938

55 Kickham, C J E, and Moloney, W C Disturbances of Bladder Function in Pernicious Anemia, *New England J Med* **218** 880, 1938

56 Yang, C S, and Chang, S L The Treatment of Neurological Manifestations of Pernicious Anemia Report of a Case, *Chinese M J* **53** 469, 1938

57 Romano, J, and Evans, J W Symptomatic Psychosis in a Case of Secondary Anemia, *Arch Neurol & Psychiat* **39** 1294 (June) 1938

58 Rotter, W, and Peña Chavarría, A The Influence of the Tropical Anemias on the Physiopathology of the Brain, *Puerto Rico J Pub Health & Trop Med* **13** 359, 1938

orders and etiologic factors (malaria and ankylostoma) must all be considered as causes of the mental disturbances

Ungley<sup>59</sup> has recently published a comprehensive review on the prevention and treatment of the neurologic manifestations. He has emphasized that an early and accurate diagnosis should be made, excess anti-anemic treatment, with the blood picture as an index, should be given, beneficial changes, if they occur, will be observed before one year, and the prognosis depends more on the duration of the illness and less on the severity of the disease and the age of the patient. He concluded that cure is a rarity and is not to be expected.

*Gastric Juice*—Although it has been adequately demonstrated that the gastric juice is an important factor in hemopoiesis, there still exist several problems related to this subject which have been unanswered. What is the intrinsic factor? Where is its source? What is its modus operandi? Morrison<sup>60</sup> has summarized the various hypothetic suggestions related to these questions but has added that further investigations are needed to evaluate the theories.

Final proof of the role of the stomach in hemopoiesis has been demonstrated by Wilkinson and his co-workers.<sup>5</sup> These investigators incubated with beef steak stomachs of patients with a normal blood picture and of patients with pernicious anemia and noted that in the former cases this was effective but not in the latter. They concluded that the "enzyme" is absent from the stomach in pernicious anemia or present in too small amounts to be detected by this method.

In regard to the source of the intrinsic factor, Magnus and Ungley<sup>3</sup> pointed out that the pathologic changes in the stomachs of patients who die of pernicious anemia are limited to the fundus. This fact is somewhat disconcerting, since it had been previously demonstrated from a histologic and a physiologic point of view that the pylorus, cardia and duodenum were the important sites of formation. It is the opinion of Uotila<sup>61</sup> that the small intestine has more antianemic principle than the stomach and that it plays an important part in the preparation of the antianemic substance. This author fed to different patients a powdered preparation made from various parts of the small intestine. He concluded that the antianemic substance was present throughout the small intestine and that its strength of activity varied in the ileum, duodenum and jejunum in decreasing order. Goodfriend, Chain and

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59 Ungley, C. C. The Prevention and Treatment of the Neurological Manifestations of Pernicious Anemia, *Clin J* **67** 5, 1938.

60 Morrison, S. Newer Interpretations and Conceptions of Gastric Mucosal Functions. Further Advances in Study of Gastric Achylia, Evidence Suggesting Role for Oxyntic Cell in Pernicious Anemia, *Internat Clin* **1** 119, 1938.

61 Uotila, U. On the Antianemic Function of the Small Intestine, *Acta med Scandinav* **95** 415, 1938.

Florey <sup>62</sup> attempted to evaluate the antianemic potency of various gastrointestinal secretions according to the method of Jacobson. They found an effective reticulocytogenic agent for guinea pigs in the pyloric, duodenal and ileal secretions of the pig and in the pyloric and duodenal contents of the rabbit and goat, this factor was absent from the fundus of the pig and cat. They are of the opinion that these findings substantiate those of Meulengracht as to the source and distribution of the intrinsic factor.

Goldhamer and Kyei <sup>63</sup> were able to salt out the intrinsic factor from hog stomach and gastric juice with ammonium sulfate. It was further observed by these authors that this substance was nondialyzable. Depepsinized gastric mucosa was found by Morrison <sup>6</sup> to be ineffective, but whole stomach mucosa contained an active erythropoietic substance. From the results obtained, this author concluded that pepsin per se is not the inactivating material, but, rather, the process of eliminating the pepsin also inactivates the mucosa. Jones and Wilkinson <sup>64</sup> attempted to determine the quantity of intrinsic factor in gastric juice by the Lasch method. They concluded that the method was unreliable and that all gastric juices showed similar activity curves as regards the  $p_H$ .

Taylor and his co-workers <sup>8</sup> studied the resemblance between the proteolytic activity of normal human gastric juice on casein in neutral solution and the activity of the intrinsic factor. When equal parts of gastric juice and a 1 per cent solution of casein was incubated at 37.5 C and at  $p_H$  7.4, there was a progressive increase in the nitrogenous substances in trichloroacetic filtrates of the digests. This activity was found to be independent of saliva or duodenal contents, it was absent or diminished in patients with pernicious anemia, the activity was not altered by Berkefeld filtration or exposure to alkali but was destroyed by heating at 40 C for seventy-two hours or at 70 to 80 C for thirty minutes or by boiling for five minutes. The activity was somewhat inhibited by  $p_H$  less than 3.5. The in vitro activity of the mixture was removed by exposure to Lloyd's reagent (specially prepared siliceous earth). The hydrolysis of casein under the conditions described progresses within twenty-four hours to proteoses and peptones, with the production of very little amino nitrogen. The authors concluded that

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62 Goodfriend, J., Cham, E., and Florey, H. W. A Reticulocytogenic Agent for Guinea Pigs Present in Certain Gastro-Intestinal Secretions, *Quart J Exper Physiol* **28** 115, 1938.

63 Goldhamer, S. M., and Kyei, J. Chemical Studies of the Intrinsic Factor in Desiccated Stomach and Normal Human Gastric Juice. I Separation of the Intrinsic Factor, *Proc Soc Exper Biol & Med* **37** 659, 1938.

64 Jones, T. S. G., and Wilkinson, J. F. Investigations on the Nature of Haemopoietin, the Anti-Anaemic Principle in Hog's Stomach. IV On the Biochemical Method of Lasch for the Quantitative Determination of the "Intrinsic Factor" in Gastric Juice, *Biochem J* **32** 1352, 1938.

the activity described is not due to pepsin, trypsin or erepsin and that the results indicate the activity of a proteolytic enzyme

Further evidence that achlorhydria is a constant feature of pernicious anemia was demonstrated by Rozendaal and Washburn<sup>65</sup> They observed 906 patients with pernicious anemia, and all had achlorhydria, in both relapse and remission In 34 instances the absence of "free" acid was observed two to twenty-one years before anemia was present, in 2 other cases, hydrochloric acid was noted seventeen to nineteen years before the anemia was observed

An excellent summary of the role of the various parts of the gastrointestinal tract in the formation of red blood cells and in the prevention of anemia has been published by Kugelmass<sup>66</sup>

#### MACROCYTIC ANEMIAS OTHER THAN PERNICIOUS ANEMIA

The relation of the gastrointestinal tract to the physiology of erythropoiesis has received considerable emphasis in the past decade The various factors which may produce macrocytic anemia have been discussed in the excellent reviews by Vaughan,<sup>67</sup> Ungley<sup>2</sup> and Davidson<sup>68</sup> It is generally accepted that the substance necessary for maturation of the red blood cells is produced by the interaction of the extrinsic and the intrinsic factor The resultant product is absorbed from the intestine, stored in the liver and released to the body tissues for utilization as needed Macrocytic anemia will result if there is a disturbance of any of the factors involved in this mechanism

Wills and her co-workers<sup>69</sup> produced macrocytic anemia in monkeys fed a deficient diet The anemia was then treated with various crude products and refined extracts prepared from liver, yeast (inarmite) and wheat germ In view of the fact that the "monkey anemia" was resistant to the highly purified extracts, whereas the crude preparations were beneficial in both pernicious and "monkey anemia," these investigators concluded that, in addition to the deficient extrinsic factor, some other substance, perhaps related to the vitamin B complex, was the causative agent in the production of "monkey anemia" Nine patients

65 Rozendaal, H M, and Washburn, R N Gastric Secretion in Cases of Pernicious Anemia, *Ann Int Med* **11** 1834, 1938

66 Kugelmass, I N The Anemias in Digestive Diseases of Children, *Arch Pediat* **55** 268, 1938

67 Vaughan, J M Anaemia and the Gastro-Intestinal Tract, *Brit M J* **2** 57, 1938

68 Davidson, L S P, and Fullerton, H W Some Rare Types of Macrocytic Anaemia, *Quart J Med* **7** 43, 1938

69 Wills, L, Clutterbuck, P W, and Evans, D B F A New Factor in the Production and Cure of Macrocytic Anemias and Its Relation to Other Hematopoietic Principles Curative in Pernicious Anemia, *Biochem J* **31** 2136, 1937



with tropical macrocytic anemia were treated by Wills and Evans <sup>4</sup> with the preparations just described, with similar results. Whereas the highly purified products were ineffective, the crude preparations produced the expected hematologic responses. Assuming that tropical macrocytic anemia and "monkey anemia" are the same, the authors concluded that although the blood pictures of pernicious anemia and tropical macrocytic anemia cannot be differentiated, the latter disease is due to some other cause in addition to the deficient extrinsic factor. They further stated that the missing substance is not vitamin B<sub>1</sub>, vitamin B<sub>4</sub>, lactoflavin or nicotinic acid.

A comprehensive study of the tropical macrocytic anemia occurring in Macedonia was made by Fairley, Bromfield, Foy and Kondi <sup>70</sup>. From their observations, these investigators suggested the term nutritional macrocytic anemia and described two types—nonhemolytic and hemolytic. The latter is the more common type. It is usually present during pregnancy and lactation, although it has been observed in males. The bone marrow shows a panmyelopathic picture, characterized by erythropoiesis with megaloblastic degeneration, pathologic precursors of the white blood cells and an abnormal condition of the megakaryocytes. The peripheral blood is characterized by megalocytic anemia with spherocytosis, leukopenia, with immature white blood cells, and a decrease in the platelet count. The last-mentioned finding was considered to be the cause of the purpura which was observed in 25 per cent of the cases. The authors concluded that the anemia is the result of a diet deficient in animal protein and fat and that the hemolysis is due to the overactivity of a chronically irritated reticuloendothelial system which is working on an abnormal red blood cell.

Bachrach and Fogelson <sup>9</sup> removed the stomach as well as a large portion of the upper part of the small intestine from dogs. These animals were observed for two years and failed to show macrocytic anemia. Petri, Nørgaard and Bing <sup>71</sup> noted several interesting pathologic changes resulting from the removal of the stomach of young swine. These animals showed, after two months, itching, signs of calcium deficiency, inhibition of growth, emaciation, warty plaques, lengthening of the rear legs, bending of the back, a staggering and stiff gait, muscular atrophy, severe microcytic anemia and terminal diarrhea. The central nervous system showed varied degenerative phenomena, especially in the spinal ganglions, but little in the peripheral nerves. It was concluded from these results that there is a specific substance in the stomach of swine,

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<sup>70</sup> Fairley, N. H., Bromfield, R. J., Foy, H., and Kondi, A. Nutritional Macrocytic Anaemia in Macedonia. A Preliminary Report, *Tr. Roy. Soc. Trop. Med. & Hyg.* **32**: 132, 1938.

<sup>71</sup> Petri, S., Nørgaard, F., and Bing, J. Pathological Changes Produced by Gastrectomy in Young Swine, *Am. J. M. Sc.* **195**: 717, 1938.

dog and man which is required to maintain the skin and nervous system in a normal healthy state. Changes in the blood occurring in man following gastric resection were studied by Jura<sup>72</sup>. It is this investigator's opinion that not only is the stomach a factor in controlling erythropoiesis but, in addition, the absorption of iron and the vicarious hemopoietic function of the small intestine are also very important.

Bianco and Jolliffe<sup>73</sup> studied the blood of 184 alcoholic addicts. Approximately 86 per cent had polyneuritis, pellagra, stomatitis, alcoholic encephalopathy, hepatic cirrhosis or anemia. In the 25 cases of noncomplicated alcoholic addiction, no anemia was noted. In 61 per cent of the cases in which there were complications, anemia was observed. Macrocytosis occurred in 50 per cent of both groups. The authors concluded that there was no correlation between the frequency of macrocytosis and achlorhydria, the severity of hepatic damage and the presence of an enlarged liver and that the macrocytosis was due to an extrinsic deficiency with respect to normocytosis and not to hepatic failure.

Macrocytic anemia related to pregnancy has been reported by Dockeray<sup>74</sup> and Atkin<sup>75</sup>. It is the former's opinion that the anemia is due to both the pregnancy and a dietary deficiency. Adams and McQuarrie<sup>76</sup> reported the case of a 2 year old girl with macrocytic anemia and temporary achlorhydria. After antianemic therapy the blood picture returned to normal and remained there. These investigators suggested that the anemia resulted from a transient functional disturbance in the mechanism involved in the elaboration and utilization of the intrinsic factor.

Richardson<sup>77</sup> observed the occurrence of macrocytic anemia in a patient after enteroenterostomy was performed. The anemia was readily controlled by parenteral therapy. A permanent cure was effected by a second operation, which eliminated the short-circuiting of the bowel.

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72 Jura, V. La variazioni dell'eritrocitosi dopo resezione gastrica per ulcera duodenale, *Policlinico (sez. chir.)* **45** 31, 1938.

73 Bianco, A., and Jolliffe, N. The Anemia of Alcoholic Addicts. Observations as to the Role of Liver Disease, Achlorhydria, Nutritional Factors and Alcohol on Its Production, *Am. J. M. Sc.* **196** 414, 1938.

74 Dockeray, G. C. Puerperal Megalocytic Anaemia, *Irish J. M. Sc.*, March 1938, p. 126.

75 Atkin, I. Post-Partum Macrocytic Anemia Associated with Confusional States, *Lancet* **1**:434, 1938.

76 Adams, J. M., and McQuarrie, I. Severe Functional Anemia in a Child, Resembling Pernicious Anemia of Adults. A Case Study, *J. Pediat.* **12** 176, 1938.

77 Richardson, W. Pernicious Anemia Due to Enteroenterostomy. *New England J. Med.* **218** 374, 1938.

Suarez<sup>78</sup> reviewed 150 cases of sprue and summarized his observations concerning the red blood cells. The average mean corpuscular volume was 123 cubic microns, the color index .122, the volume index 1.39, the mean corpuscular hemoglobin value 36.6 micromicrograms, the hemoglobin value 66 per cent and the red blood cell count 2,710,000 per cubic millimeter. The bone marrow was normoblastic, although megaloblasts were present. The author believes that sprue is primarily a blood dyscrasia.

Several experiments were performed by Schiff and his colleagues<sup>13</sup> to determine the presence or absence of the hemopoietic principle in the liver of patients who clinically had exhibited macrocytic anemia. Their conclusions substantiated the work of other investigators, who had previously demonstrated the presence of the active principle in the diseased liver. Schalm,<sup>79</sup> employing the diffraction method of measurement of red blood cells, observed macrocytosis when damage to the hepatic parenchyma was present.

Achrestic anemia from a clinical and hematologic point of view has been carefully reviewed by Wilkinson.<sup>80</sup> Some cases of anomalous hyperchromic anemia have been reported by Israels and Wilkinson.<sup>81</sup> These authors have pointed out the various characteristic changes in the bone marrow which occur in aleukemic leukemia, aplastic anemia and achrestic anemia and how they may be differentiated from the other types of macrocytic anemia. Zanaty<sup>82</sup> also has studied the bone marrow in cases of achrestic anemia and has stated that this disease is not a distinct clinical entity but rather a form of aplastic anemia.

The type of treatment necessary to alleviate the various macrocytic anemias has been thoroughly summarized by Bell.<sup>83</sup> If the intrinsic or extrinsic factors are absent, oral medication may be effective, however, if there is a disturbance in absorption or storage, parenteral therapy should be instituted. Specific treatment should also be given for any other deficiencies which may exist.

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78 Suarez, R. M. Clinical and Hematological Review of Sprue Based on the Study of One Hundred and Fifty Cases, *Ann Int Med* **12** 529, 1938.

79 Schalm, L. The Average Red Blood Cell Diameter in Liver Disease and Jaundice, *Acta med Scandinav* **93** 512, 1938.

80 Wilkinson, J. F. L'anémie achrestique, *Rev belge sc méd* **10** 191, 1938.

81 Israels, M. C. G., and Wilkinson, J. F. Some Anomalous Hyperchromic Anaemias, *Lancet* **2** 362, 1938.

82 Zanaty, A. F. Sternal Puncture in Pernicious and Achrestic Anaemia, *Lancet* **2** 1365, 1937.

83 Bell, J. A. The Modern Treatment of Pernicious Anaemia and Associated Macrocytic Anaemias, *South African M J* **12** 547, 1938.

## HEMOLYTIC JAUNDICE

The various types of hemolytic jaundice have many common features, but it is often difficult to determine the cause. The usual characteristics of the congenital type are anemia, enlargement of the spleen, jaundice, a history of exacerbations and remissions, microcytosis, spherocytosis, increased fragility of the red blood cells and constant reticulocytosis. Dyke and Young<sup>84</sup> described 6 cases of macrocytic hemolytic anemia, which is thought by them to be a distinct clinical entity. In spite of the fact that it has many features similar to the congenital type, it differs in that there is no family history of the disease, the anemia usually occurs after the age of 30 years, the red blood cells are large and there is a poor response to splenectomy. Israels and Wilkinson<sup>85</sup> observed the clinical course of hemolytic jaundice occurring in adults. They pointed out that in their series the outstanding feature was an unusual histiocytic reaction in the spleen. Two cases of acute hemolytic anemia in which a ready response to transfusions was obtained were reported by Greenwald<sup>86</sup>. It is the author's opinion that the disease is due to the introduction or evolution of some hemolytic substance in the blood. He based this assumption on the fact that the bone marrow appeared normal.

A similar conclusion based on experimental work was suggested by Dameshek and Schwartz<sup>87</sup>. These investigators discovered isohemolysis of the immune body type in 3 cases of acute hemolytic anemia. A serum possessing similar immunologic properties was prepared by the injection of red blood cells from guinea pigs into rabbits. By injection of variable doses of this hemolytic serum into experimental animals, several types of hemolytic anemia were produced. Examination of the blood revealed microspherocytosis, increased fragility of the red blood cells, reticulocytosis and "pseudomacrocytic" blood pictures. The authors believe that the spherocytosis is due to the hemolysins and not to any abnormal anatomic peculiarities or to a disturbed formation of the red blood cells in the bone marrow. They added that the hemolytic syndromes are due to the hemolysins (endogenous origin), possibly of different types, varying in amounts and acting differently in degree, the

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84 Dyke, S. C., and Young, F. Macrocytic Haemolytic Anaemia Associated with Increased Red Cell Fragility, *Lancet* **2** 817, 1938.

85 Israels, M. C. G., and Wilkinson, J. F. Haemolytic (Spherocytic) Jaundice in the Adult, *Quart J Med* **7** 137, 1938.

86 Greenwald, H. M. Acute Hemolytic Anemia, *Am J M Sc* **196** 179 1938.

87 Dameshek, W., and Schwartz, S. O. Hemolysins as the Cause of Clinical and Experimental Hemolytic Anemias, with Particular Reference to Nature of Spherocytosis and Increased Fragility, *Am J M Sc* **196** 769, 1938, The Presence of Hemolysins in Acute Hemolytic Anemia. A Preliminary Note, *New England J Med* **218** 75, 1938.

resulting changes in the blood are dependent on the hemolysins, their nature and amount, and the reaction to them

Acquired hemolytic jaundice, with its various characteristic diagnostic features, has been reported on by Rastetter and Murphy<sup>88</sup> They have pointed out that the onset is abrupt, the course rapid, the cause usually not known and remissions not unusual Pain and fever differentiate it from the congenital type The blood findings are the same as those observed in familial acholuric jaundice Hemolytic anemia resulting from sulfanilamide therapy was not noted by Wood<sup>89</sup> and by Lockwood and his co-workers<sup>90</sup>

Pepper<sup>91</sup> has made an excellent survey of the so-called hemolytic anemias and has stated that it is difficult to differentiate them He has suggested that they be classified according to the mechanism of production, namely (1) a fault in the erythrocyte, (2) parasitic destruction, (3) an allergic reaction, (4) a chemical, (5) a bacterial toxin, (6) some unknown mechanism (7) specific hemolysins, (8) physical agents, (9) overactivity of the reticuloendothelial system and (10) phagocytosis

In recent years spherocytosis and the size of the red blood cells have received considerable attention In view of the globular form the red blood cells in hemolytic jaundice, the majority of them are near the point of hemolysis and readily exhibit this tendency when placed in hypotonic saline solution Dacie and Vaughan<sup>92</sup> have carefully studied the various intrinsic and extrinsic factors which influence the fragility of the red blood cells Of the intrinsic factors, the relation of the mean corpuscular thickness to the mean corpuscular diameter and the chemical composition of the cell and its membrane are the most important The extrinsic factors which influence the fragility are the oxygen and carbon dioxide content of the blood, the temperature and  $p_H$  of the hemolytic solution and the concentration of the red blood cells Hill<sup>93</sup> has also made careful observations on the dimensions of the

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88 Rastetter, J W, and Murphy, F D Acquired Hemolytic Jaundice, *Am J Digest Dis & Nutrition* **4** 805, 1938

89 Wood, W B Anemia During Sulfanilamide Therapy, *J A M A* **111** 1916 (Nov 19) 1938

90 Lockwood, J S, Coburn, A F, and Stokinger, H E Studies on the Mechanism of the Action of Sulfanilamide I The Bearing of the Character of the Lesion on the Effectiveness of the Drug, *J A M A* **111** 2259 (Dec 17) 1938

91 Pepper, O H P A Survey of the So-Called Hemolytic Anemias, *Ann Int Med* **12** 796, 1938

92 Dacie, J V, and Vaughan, J M The Fragility of the Red Blood Cells Its Measurement and Significance, *J Path & Bact* **46** 341, 1938

93 Hill, J M Dimensions of the Red Cells in Familial Hemolytic Anemia, with Particular Reference to Atypical Cases, *J A M A* **111** 2179 (Dec 10) 1938

red blood cells in familial hemolytic anemia. He concluded that microcytosis and spherocytosis were present in more than 75 per cent of the cases, spherocytosis may be absent in the presence of complications (cirrhosis of the liver), macrospherocytosis may occur during a crisis, and there is no significant correlation between the globular form of the cell and the severity of the disease, the onset of the crisis, the rapidity of regeneration or the effect of splenectomy.

In a series of well controlled experiments, Rhoads and his colleagues<sup>94</sup> demonstrated the hemolytic effect of indole on dogs fed normal diets and the increased susceptibility of the red blood cells to hemolysis in dogs fed deficient diets and indole. Observations were made on the total amount of bile excreted and the various changes which occurred in the peripheral blood. By this method a fairly accurate index was established concerning the amount of hemolysis which was produced. Josephs<sup>95</sup> has made some interesting observations on patients with various types of hemolytic anemia. He studied the course of the disease (crisis) by the method of balancing blood formation (reticulocytosis) against blood destruction (urobilin excretion expressed in relation to the total circulating hemoglobin). After a sudden increase in the rate of hemolysis, there is usually a delay in a compensatory increase in erythropoietic activity, which accounts for one factor in the severity and prolongation of the crisis. From an analysis of his cases and those reported in the literature there appear to be two factors which influence the rapidity with which increased activity occurs. The first is dependent on antecedent activity (congenital type), which tends to shorten the period of delay. The second element is the nature of the hemopoietic disturbance, which may lengthen the period or prevent a response.

After transfusions which tended to terminate the activity of an acute hemolytic process, Josephs<sup>96</sup> noted a decrease in the urobilin content of the stools and often an increase in the red blood cell count. The latter event does not always occur. The author interpreted this finding as denoting a plasma substance which influences hemolysis. It is not soluble in ether and appears to be effective in minute amounts. When a similar substance prepared from pig's plasma<sup>97</sup> was used in 4 cases, conflicting results were obtained.

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94 Rhoads, C. P., and Barker, W. H. The Hemolytic Effect of Indol in Dogs Fed Normal Diets, *J. Exper. Med.* **67** 267, 1938. Rhoads and Miller<sup>15</sup> Rhoads, Barker and Miller<sup>16</sup>

95 Josephs, H. W. Studies in Haemolytic Anaemia. I. Haemolysis, Compensatory Regeneration and Erythroblastosis, *Bull. Johns Hopkins Hosp.* **62** 25, 1938.

96 Josephs, H. W. Studies in Haemolytic Anaemia. II. The Presence of an Anti-Haemolytic Factor in Human Plasma, *Bull. Johns Hopkins Hosp.* **62** 53, 1938.

97 Josephs, H. W., and Winocur, P. Studies of Haemolytic Anaemia. III. Pig's Plasma as a Source of Anti-Haemolytic Factor, *Bull. Johns Hopkins Hosp.* **62** 70, 1938.

In view of the multiple causes of hemolysis, it is necessary to determine the exact cause before therapy can be instituted. Transfusions are often invaluable before and after operation, but, as pointed out by Sharpe and Davis,<sup>98</sup> the hemolytic process may be exaggerated by this therapeutic procedure. In the congenital type, splenectomy is indicated, and, as suggested by Anderson,<sup>99</sup> the purpose of the operation is to restore the balance between production and destruction of red blood cells.

#### SICKLE CELL AND ERYTHROBLASTIC ANEMIA

According to Josephs,<sup>95</sup> in studying hemolytic anemia, in which he included the sickle cell variety, it is necessary to measure the rate of formation and destruction of blood. The urobilin excretion in the stools can be used as an index of blood destruction and the number of reticulocytes in the circulating blood as an indication of blood formation. The validity of these indexes is questioned by some for the following reasons: 1. With a rising hemoglobin value, it is possible that some products of pigment catabolism may be utilized in the body to form hemoglobin. If this occurred, the urobilin excretion would not be an accurate index of blood destruction at these times. 2. If the presence of erythroblasts indicates difficulty on the part of the hemopoietic system in maturing red blood cells, the reticulocyte count might not be an accurate index of the formation of red blood cells.

While there is no definite proof that excretion of urobilin measures blood destruction, it can be said that in individual cases it acts as if it were approximately proportional to the rate of blood destruction. It must be admitted that hemoglobin or its precursors may be produced more rapidly than they can be utilized. When this occurs they would be excreted as excess pigment products. Obviously, under such conditions the urobilin value would not be an index of erythrocytic destruction. Another possibility which would vitiate the urobilin value as an index of blood destruction is that erythrocytic destruction might occur before the cells entered the circulation. Nevertheless, Josephs in reporting his work, based it on the proposition that urobilin excretion measures blood destruction and believes that this explains adequately the fluctuations in the values for erythrocytes and hemoglobin.

He believes not only that there is a relation between blood destruction as indicated by urobilin excretion but that blood formation may be measured by the percentage of circulating reticulocytes. This relation,

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<sup>98</sup> Sharpe, J. C., and Davis, H. H. Severe Reactions Following Transfusion in Hemolytic Jaundice. Report of Two Cases, *J. A. M. A.* **110** 2053 (June 18) 1938.

<sup>99</sup> Anderson, P. M. Anaemia Cured by Splenectomy, *M. J. Australia* **1** 385, 1938.

however, is "completely shattered" by the presence of erythroblasts. Erythroblastosis, "while often associated with greatly increased hemolysis, is not strictly dependent upon the rate of blood destruction, but constitutes a third variable and is an expression of a pathological process which affects maturation of red cells, and by so doing disturbs the ability of the erythropoietic tissue to respond effectively to the need for red cell replacement." Erythroblastosis may well be in part due to an increased need for blood formation, but it must also be considered as evidence of a disturbance of erythropoietic function.

In patients with sickle cell anemia and congenital hemolytic jaundice, the blood becomes stabilized at a constant level for long periods. In sickle cell anemia this equilibrium is less stable and at a lower level, so that the patient is more incapacitated.

It is believed by Josephs that in congenital hemolytic jaundice the process is predominantly hemolytic, whereas in Mediterranean anemia it is predominantly erythroblastic, sickle cell anemia is considered as occupying an intermediate position between the two. In a study of crises in hemolytic anemia, it was found that after a sudden increase in hemolysis, there was usually a delay in erythropoietic activity which was an important factor in the severity and duration of a crisis. This delay appeared to be influenced by (1) antecedent activity, which apparently shortened it, and (2) a hemopoietic disturbance, which might prolong it.

In a second paper Josephs<sup>96</sup> studied an antihemolytic factor in human plasma. This study had its inception in a "more or less" chance finding that after a patient with sickle cell anemia had been given a transfusion, there was a striking decrease in the excretion of urobilin. His studies indicated that normal plasma contains a substance which reduces the rate of blood destruction in sickle cell anemia and probably in congenital hemolytic jaundice. This substance is present in the ether-soluble fraction of protein-free plasma and is effective in minute amounts. It is suggested that in sickle cell anemia and perhaps in congenital hemolytic jaundice this substance may be lacking, and as a result the normal equilibrium between blood formation and blood destruction is disturbed.

A third paper, by Josephs and Winocur,<sup>97</sup> is concerned with a study of pig's plasma as a source of the antihemolytic factor. The material utilized was prepared as follows. The proteins of pig's plasma were precipitated with 95 per cent alcohol, the alcoholic solution was evaporated in a vacuum, the residue was extracted with alcohol, concentrated, filtered and evaporated to dryness, and the lipoids were extracted with ether. The residue was then taken up with alcohol. This alcoholic solution was then concentrated and administered intramuscularly. The value of urobilin excretion, in milligrams per gram of hemoglobin was utilized as an index of the value of the preparation in controlling hemolysis. It was considered that the normal excretion is between 0.2



and 0.4 mg per gram of hemoglobin and that an excretion of 5 mg indicates a moderate degree of hemolysis in sickle cell anemia, an excretion of 10 to 15 mg, a relatively severe process, and excretions of over 20 mg, an extremely severe hemolysis, typical of a hemolytic crisis. Studies of the effect of injection of this substance were made on 4 patients with sickle cell anemia. Some of them showed "a good therapeutic effect," and it is hoped that in the future these plasma concentrates will be found to be more effective.

Weil<sup>100</sup> described Fanconi's anemia in 2 brothers, aged 7 and 13 years, respectively. The symptoms differed from those of Addisonian pernicious anemia in that there was no increased bilirubinemia, achlorhydria was absent after injection of histamine and improvement did not result from liver therapy. One of the brothers showed endocrine disturbance with obesity, possibly associated with a hypophyseal or thymic pathologic condition. A third, sporadic case, in a girl of 6 years, was described. Anemia and leukopenia were accompanied by pigmentation of the skin, congenital malformation of the thenar eminences and obesity (trunk).

Hellman and Hertig<sup>101</sup> studied the placentas of 16 infants suffering from erythroblastosis of the hydropic variety and 7 of the icterus gravis type. Pathologic changes in the epithelium, stroma and vascular tree were present in the placentas in both varieties but were less advanced in the placentas of infants suffering from erythroblastosis of the icterus gravis variety. The changes are considered specific for these diseases.

#### CHANGES IN THE BLOOD ASSOCIATED WITH INFECTION

Although the interpretation of the changes in the blood associated with infection has been of extreme importance clinically, little is known concerning the production of the anemia which is often present. The anemia may be macrocytic or microcytic, the latter being the more common type. Cases of acute hemolytic anemia have been reported by Baxter and Everhart,<sup>102</sup> Mendels,<sup>103</sup> Greenthal<sup>104</sup> and Tangredi<sup>105</sup>. All

100 Weil, P. E. Myelose aplasique infantile familiale avec malformations et troubles endocriniens. Contribution a l'etude du syndrome de Fanconi, *Sang* **12** 369, 1938.

101 Hellman, L. M., and Hertig, A. T. Pathological Changes in the Placenta Associated with Erythroblastosis of the Fetus, *Am J Path* **14** 111, 1938.

102 Baxter, E. H., and Everhart, M. W. Acute Hemolytic Anemia (Lederer Type), *J. Pediat* **12** 357, 1938.

103 Mendels, J. Acute Hemolytic Anemia (Lederer), *Nederl tijdschr v geneesk* **82** 536, 1938.

104 Greenthal, R. M. Acute Hemolytic Anemia Developing During Streptococcus Sepsis. Report of a Case in Which Sulfanilamide Was Given After Anemia Had Developed, *J. Pediat* **12** 517, 1938.

105 Tangredi, G. Anemia emolitica sub-acute febbrile, a tipo pernicioso e con epato-splenomegalia (forma del Lederer?), *Haematologica* **19** 171, 1938.

these authors are in agreement as to the clinical course of the disease. Persons of any age or of either sex may be afflicted. The onset is usually sudden and characterized by headaches, gastrointestinal upsets, abdominal pain and, after an incubation period of two to six days, severe anemia, pallor, icterus and fever. Splenic<sup>106</sup> or hepatic enlargement may or may not be present. The anemia is of the macrocytic type, with evidence of regeneration. The cause of the disease has not been definitely established. Infection has been considered by the majority<sup>107</sup> to be the fundamental cause, although Baxter and Everhart<sup>102</sup> suggested the possibility of allergy.

The accepted form of treatment is by means of multiple transfusions. Greenthal described the successful use of sulfanilamide as well as transfusions in his case and pointed out the fact that sulfanilamide may prolong the anemia and should be administered with care.

Shiskin and Gloyne<sup>106</sup> studied the importance of anemia as a predisposing factor in tuberculosis. Rabbits were made anemic by bleeding and then infected with human and bovine tubercle bacilli. Appreciable differences in the animals with and without anemia were not observed.

The clinical importance in infection of the numerical, cytoplasmic and nuclear alterations of the neutrophils has been emphasized frequently. Watson and Sarjeant<sup>108</sup> have stressed the fact that in pyogenic infections the earliest changes are leukocytosis and a predominance of young neutrophils (a shift to the left). With suppuration and progression of the infection, the white blood cells are withdrawn from the circulation faster than they are produced by the bone marrow, and leukopenia results. In uncomplicated pneumonia there is a parallel increase in the total white blood cell and the polymorphonuclear leukocyte count, in complicated pneumonia the neutrophil count is relatively increased, but leukopenia is present.

Nettleship<sup>109</sup> produced inflammatory changes in the skin of the rabbit and observed early severe leukocytosis. Cytoplasmic changes in the neutrophils occurred within two hours. Only the leukocytes showed necrosis early. The author believes some breakdown product, resulting from the action of the injuring agent on the peripheral tissue, diffuses into the blood stream and causes leukocytosis and hyperplasia of the bone marrow.

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106 Shiskin, C, and Gloyne, S. R. Anaemia as a Predisposing Factor in Tuberculosis, *Am Rev Tuberc* **38** 325, 1938.

107 Mendels<sup>103</sup> Greenthal<sup>104</sup> Tangredi<sup>105</sup>

108 Watson, C. H., and Sarjeant, T. R. The Significance of a Low Leucocyte Count in Acute Pyogenic Infections, *Canad M A J* **39** 460, 1938.

109 Nettleship, A. Leucocytosis Associated with Acute Inflammation, *Am J Clin Path* **8** 398, 1938.

The total white cell count not only is of diagnostic and prognostic value in infections but has been considered by many as an important aid in the study of allergic conditions. Rusten<sup>110</sup> has stated that the leukopenic index is of value in atopic dermatitis only as regards food. Hill and Nethery<sup>111</sup> have pointed out the many technical difficulties associated with the leukopenic index but are of the opinion that the test is of considerable value when properly controlled. That all authors are not in agreement as to the diagnostic value of the leukopenic index can be judged from the observations of Brown and Wadsworth,<sup>112</sup> as well as those of Loveless, Dorfman and Downing.<sup>113</sup> The first group of dissenting investigators have pointed out that there is no mathematical justification for the test. The second group of observers have noted a reduction in the total white blood cell count in nonsensitive as well as in sensitive patients. Hence, the value of the test is questionable.

#### ANEMIA ASSOCIATED WITH CANCER

Carcinomatosis, especially that of the vital organs, is usually associated with anemia. The anemia may be mild or severe, macrocytic or microcytic, but it is not pathognomonic, nor does it give any information as to the site or the extent of the malignant process. Leukocytosis may often be observed. Alteration of the number of platelets in the peripheral blood is not a constant feature, the number may be increased, decreased or normal.

The etiologic factors of the associated anemia are multiple. Microcytic anemia has been ascribed to a disturbance in iron metabolism (failure of absorption or chronic hemorrhage). Welch, Mayo and Wakefield<sup>114</sup> studied pathologic specimens of the colon on the right side, proximal and distal to the malignant process. They observed no significant changes in the mucosa, submucosa or muscular coats of the large intestine. The ileum likewise appeared to be normal on microscopic observation. Hence, it was their opinion that whatever the cause of the anemias associated with carcinoma of the bowel, they were not due to objective structural changes proximal to the lesion in the colon or in the terminal portion of the ileum with subsequent interference of the absorption of iron.

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110 Rusten, E. M. The Leukopenic Index Test in Atopic Dermatitis, *Arch Dermat & Syph* **37** 52 (Jan) 1938.

111 Hill, J. M., and Nethery, E. B. The Variations in the Leucocyte Count in Relation to the Leucopenic Index, *J Allergy* **9** 371, 1938.

112 Brown, E. A., and Wadsworth, G. P. The Leucopenic Index, *J Allergy* **9** 345, 1938.

113 Loveless, M., Dorfman, R., and Downing, L. A Statistical Evaluation of the Leucopenic Index in Allergy, *J Allergy* **9** 321, 1938.

114 Welch, C. S., Mayo, C. W., and Wakefield, E. G. A Histologic Study of the Intestine Proximal to Carcinoma of the Right Side of the Colon, Associated with Anemia, *Surgery* **2** 849, 1937.

Anemia complicating carcinoma of the pharynx and associated with dysphagia was noted by McGibbon<sup>115</sup> He reported this occurrence in members of three generations of one family and stressed the fact that heredity is a most important factor He also pointed out that dysphagia and anemia are rare in males

Macrocytic anemia associated with gastric carcinoma may result from metastasis to the bone marrow, the coincidental existence of pernicious anemia and cancer or, as has been demonstrated by Goldhamer,<sup>116</sup> the failure of the malignant gastric tissue to produce the intrinsic factor Owing to the frequent difficulty in differentiating pernicious anemia and gastric neoplasm, roentgenograms of the gastrointestinal tract are indicated as a routine This procedure is of especial value in cases of macrocytic anemia not associated with symptoms of degeneration of the central nervous system

#### ANEMIA ASSOCIATED WITH ENDOCRINE DYSFUNCTION

The anemia associated with thyroid dyscrasias has long been a subject of controversy Many authors have observed macrocytic anemia with diminished thyroid function, while others have noted microcytic anemia The anemia may be directly related to the dysfunction of the thyroid gland, or it may exist as an independent condition Bomford<sup>117</sup> studied 10 cases of myxedema associated with anemia He stated that the reduced number of red blood cells and the hemoglobin value are a physiologic adaptation to diminished oxygen need by the tissues, and thyroxine is not a requisite for hemopoiesis in the bone marrow Parsons,<sup>118</sup> on the other hand, suggested that the thyroid hormone is necessary for red blood cell metabolism In accordance with this view, Jaffé<sup>119</sup> described the pathologic changes in a case of severe aplastic anemia associated with sclerosis of the thyroid gland The functional glandular tissue was completely replaced by dense scar tissue, and the bone marrow was aplastic

Meyers and his co-workers<sup>120</sup> have carefully analyzed a series of cases of hypochromic anemia in women and have pointed out that hypo-

115 McGibbon, J E G Pharyngeal Carcinoma and Dysphagia with Anemia Occurring in Three Generations of One Family, *J Laryng & Otol* **53** 32, 1938

116 Goldhamer, S M Macrocytic Anemia in Cancer of the Stomach, Apparently Due to Lack of Intrinsic Factor, *Am J M Sc* **195** 17, 1938

117 Bomford, R Anaemia in Myxoedema and the Role of the Thyroid Gland in Erythropoiesis, *Quart J Med* **7** 495, 1938

118 Parsons, L G Nutrition and Nutritional Diseases *Lancet* **1** 65, 1938

119 Jaffe, R H Severe Anemia of the Aplastic Type Associated with Sclerosis of the Thyroid Gland, *Arch Int Med* **61** 19 (Jan) 1938

120 Meyers, S G, Price, A H, Mack, H C, Foster, L J, and Sharp, E A Chronic Hypochromic Anemia in Women Its Gastrointestinal Gynecologic, Endocrine and Psychiatric Features, *Ann Int Med* **11** 1590, 1938

thyroidism was present in approximately 50 per cent. Disregarding the controversy as to the cause of the anemia associated with myxedema, Sharpe and Bisgard<sup>121</sup> clearly demonstrated in thyroidectomized rabbits that the resulting anemia readily responded to thyroid medication but could not be influenced by liver or iron. Bomfort reported similar conclusions from his clinical data.

A new syndrome that is apparently related to the posterior lobe of the pituitary gland has been described by Jones<sup>122</sup>. The important clinical features are hypertension, hyperchromic anemia, achlorhydria and an abnormal carbohydrate tolerance. The author has attributed the altered metabolism to hyperfunction of the posterior lobe. Flaks and his co-workers<sup>123</sup> have offered the opinion that hemopoiesis is regulated by a hypophysial hormone. After removal of the hypophysis of rats, the bone marrow atrophied, and there was resulting anemia. These changes could be reversed with parenteral injections of hypophysial extract.

#### IRON DEFICIENCY

*Iron Metabolism and Experimental Anemia*—In the entire field of physiology there appears to be least established information, most speculation and most divergence of opinion on the subject of iron metabolism. A reason for this lies in the attempt to treat iron as a substance included in the daily quantitative interchange between the organism and its environment. On the basis of this unsupported and unjustified assumption, balance studies have been carried out, and an effort has been made to apply the results of observations of intake and loss during periods of constant diet to the findings obtained after the administration of disproportionately large supplements of medicinal iron. An investigation of balance applied to a substance required for nutrition implies, for its validity, that such a substance is absorbed and excreted under controlling mechanisms which, in turn, are governed by the metabolic requirements of the organism or which may, as the result of disease, depart from such requirements. In the case of iron, no such controlling mechanisms have been demonstrated. Widdowson and McCance<sup>124</sup> studied the intake and output of iron of healthy men and

121 Sharpe, J. C., and Bisgard, J. D. The Thyroid Gland and Hematopoiesis. II. The Effect of Thyroid Extract, Liver Extract, and Iron on the Anemia of Myxedema, *J. Lab. & Clin. Med.* **23** 219, 1937.

122 Jones, E. I. A New Syndrome Apparently Due to Overactivity of the Posterior Pituitary, *Lancet* **1** 11, 1938.

123 Flaks, J., Himmel, I., and Zotnek, A. La polyglobulie provoquée par les extraits de lobe antérieur d'hypophyse prouve l'existence d'une hormone hémoïétique, *Presse med.* **46** 1506, 1938.

124 Widdowson, E. M., and McCance, R. A. The Absorption and Excretion of Iron Before, During and After a Period of Very High Intake, *Biochem. J.* **31** 2029, 1937.

women While receiving between 6 and 9 mg of blood iron daily these persons were in balance When the oral intake was increased by dietary changes to 12 to 16 mg, the subjects remained in balance, but when 1 Gm of medicinal iron was given daily in the form of iron and ammonium citrates, a net absorption, over a period of a few weeks, of 1.5 to 5.0 Gm of the metal was registered Subsequently, without loss of the previously retained iron, the subjects were in balance on diets low in iron The same authors<sup>125</sup> demonstrated that when 7 mg of iron daily was given intravenously to normal subjects, none of the metal was excreted These observations support their hypothesis that the intestine has no power of regulating by excretion the amount of iron in the body This conclusion has much to recommend it, although it is in disagreement with earlier experimental studies of iron excretion and with the recent work of Nakamura,<sup>126</sup> Kamano<sup>127</sup> and Chin,<sup>128</sup> who found evidence by microchemical methods of the epithelial excretion of iron, respectively, in the stomach, small and large intestine and cecum of rabbits after its intravenous and oral administration The explanation of intestinal absorption of iron offered by Widdowson and McCance on the basis simply of gross imbalance between the concentration of the metal in the intestinal contents and that in the circulating blood within the intestinal capillaries explains their observation of iron retention by normal subjects when large medicinal supplements were given and is also in accord with the studies<sup>129</sup> on iron retention by Fowler and Barer and by Brock and Hunter but cannot be reconciled with the conclusions of Reimann, Fritsch and Schick A recent study by Fowler and Barer<sup>130</sup> of the absorption of iron by patients with pernicious anemia, lead poisoning and myxedema, conditions in which, clinically, iron deficiency is believed to play no part, demonstrated a retention of from 25 to 34 per cent of the orally administered medicinal iron, an amount comparable to that retained in hypochromic anemia On the other hand, a preliminary report by Hahn and his associates<sup>131</sup>

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125 McCance, R. A., and Widdowson, E. M. Absorption and Excretion of Iron Following Oral and Intravenous Administration, *J. Physiol.* **94** 148, 1938

126 Nakamura, A. Ueber die Eisenausscheidung des Magens bei erwachsenem Kaninchen, *Tr. Soc. path. jap.* **28**:502, 1938

127 Kamano, M. Ueber die Eisenausscheidung des Dunndarms und Dickdarms, *Tr. Soc. path. jap.* **28**:505, 1938

128 Chin, S. Untersuchung über die Eisenausscheidung und Eisenresorption in Coecum, *Tr. Soc. path. jap.* **28** 509, 1938

129 Bethell, F. H., Isaacs, R., Goldhamer, S. M., and Sturgis, C. C. Blood A Review of the Recent Literature, *Arch. Int. Med.* **61** 923 (June) 1938

130 Fowler, W. M., and Barer, A. P. Iron Retention in Pernicious Anemia, Lead Poisoning and Myxedema, *Arch. Int. Med.* **61** 401 (March) 1938

131 Hahn, P. F., Bale, W. F., Lawrence, E. O., and Whipple, G. H. Radioactive Iron and Its Metabolism in Anemia, *J. A. M. A.* **111** 2285 (Dec. 17) 1938

of the metabolism of radioactive iron indicated that the metal was absorbed, retained and soon utilized in hemoglobin synthesis by dogs rendered anemic by repeated bleeding but that only slight absorption occurred in the case of nonanemic dogs. The question of whether iron is absorbed solely on the basis of its concentration and chemical state within the intestine (Widdowson and McCance) or whether such absorption is governed by a mechanism responsive to the body's needs (Whipple and his associates) awaits convincing answer, but the use of radioactive iron should prove a valuable tool in the solution of this and other problems of iron metabolism.

Experimental studies of anemia related to deficient formation of hemoglobin have for some time included investigation of substances which may either affect the utilization of iron in anemia or play a direct role in the synthesis of hemoglobin. The earlier work of the investigators at the University of Wisconsin on the part played by copper in the nutritional anemia of growing rats has been extended by Potter, Elvehjem and Hart<sup>132</sup> to include a study of dogs. They produced anemia in growing dogs by means of exclusive milk diets and cured the anemia with iron and copper supplements. Subsequently, 2 of the dogs were depleted of iron and copper by repeated bleeding, the consequent anemia responded poorly to iron given alone in a daily dose of 30 mg, but on the addition of 4 mg daily of copper, regeneration of hemoglobin proceeded rapidly. They found that an increase in the copper content of the blood was associated with accelerated hemopoiesis, and they concluded that copper is required by dogs for regeneration of hemoglobin. This view of the importance of copper is not shared by Hahn and Whipple,<sup>133</sup> who stated that no evidence of a deficiency of copper can be demonstrated in man or the dog. In the same communication these authors attacked the conception of "available iron," that portion of food iron which can be separated from the total iron content, by means of the dipyrindyl reaction, as being devoid of physiologic significance. They pointed out that by this method iron salts are 100 per cent "available" but that only about 35 per cent of that given orally to anemic dogs is absorbed. However, in comment, it should be pointed out that no claim has been made that the dipyrindyl test or any other chemical procedure can determine the actual absorption of orally administered iron but only that it may indicate the amount of the metal which, in appropriate circumstances, is available for absorption. The value of the dipyrindyl

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132 Potter, V R, Elvehjem, C A, and Hart, E B. Anemia Studies with Dogs, *J Biol Chem* **126** 155, 1938.

133 Hahn, P F, and Whipple, G H. Iron Metabolism in Experimental Anemia. "Availability of Iron," *J Exper Med* **67** 259, 1938.

method lies in its application to the study of the requirements for nutritional iron and not to determinations of the efficacy of preparations of medicinal iron

Bioassay of the availability of iron in food materials, carried out on rats with "milk anemia," has failed to yield uniform results in different laboratories. An attempt has been made by Smith and Otis<sup>134</sup> to explain these discrepancies as due to the varying content of copper in the anemia-producing diets. They have contended that iron depletion can be complete only when copper is given during the period of development of anemia and that part of the hemoglobin response during the curative study depends on the copper supplied by the food under assay rather than on its content of available iron. Harris and Poland<sup>135</sup> were unable to confirm these observations and concluded from their experimental results that supplementing the basal diet with copper during the production of anemia does not significantly affect the time or the severity of iron depletion, nor does it affect the hemoglobin response to subsequent iron feeding.

Cobalt is probably concerned with the metabolism of iron in sheep in much the same manner that copper appears to function in rats. Previously recognized anemia of sheep in Australia and New Zealand, attributed to cobalt deficiency, has been described by Corner and Smith<sup>136</sup> as occurring in Scotland. By means of controlled experiments they demonstrated the relation of cobalt deficiency to hypochromic anemia in sheep and found that the defect could not be eliminated with copper supplements. There was no depletion of iron reserves in the anemic animals, but medicinal iron may be effective because of its contamination with cobalt.

The effect of diets low in iron on the blood of pregnant rats and their offspring was studied by Alt<sup>137</sup>. When receiving an exclusive diet of whole milk powder, the rats failed to become anemic during the first pregnancy, but the stores of iron were depleted. During a second pregnancy moderate anemia occurred in such animals. The members of the first litter possessed normal hemoglobin values at birth and failed to show anemia during the suckling period, but those of the second

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134 Smith, M. C., and Otis, L. Hemoglobin Regeneration in Anemic Rats in Relation to Iron Intake, with Suggestions for the Improvement of Bioassay Technic for Measuring Available Iron, *J. Nutrition* **13** 573, 1937, Effect of Adding Copper to Exclusive Milk Diet Used in Preparation of Anemic Rats upon Their Subsequent Response to Iron, *ibid* **14** 365, 1937.

135 Harris, P. L., and Poland, G. L. The Effect of Copper in the Production of Nutritional Anemia in Rats, *Science* **87** 45, 1938.

136 Corner, H. H., and Smith, A. M. The Influence of Cobalt on Pine Disease in Sheep, *Biochem. J.* **32** 1800, 1938.

137 Alt, H. L. Iron Deficiency in Pregnant Rats. Its Effect on the Young, *Am. J. Dis. Child* **56** 975 (Nov.) 1938.



litter had low hemoglobin levels at birth. Iron supplements during pregnancy protected the mothers and offspring against anemia and depletion of iron reserves, whereas the addition of copper had no apparent effect on the results.

Fouts and his associates<sup>138</sup> maintained puppies in good health after weaning on a diet containing purified casein, thiamin, riboflavin, liver extract supplying nicotinic acid and extract of rice polishings supplying the rat antidermatitis factor, vitamin B<sub>6</sub>. When the B<sub>6</sub> factor was omitted from the diet, microcytic and hypochromic anemia, together with marked systemic changes, including hepatic lipoidosis, developed in the puppies. The anemia failed to respond to iron therapy but was cured by the addition of the B<sub>6</sub> factor.

Anemic dogs with renal biliary fistulas were shown by Hawkins and his associates<sup>139</sup> to suffer impairment of their capacity for hemoglobin production. The utilization of orally administered iron salts, food iron and liver amounted to half that found to occur in anemic dogs without biliary fistulas, but the utilization of intravenously administered iron in the formation of new hemoglobin was apparently unaffected by the loss of bile. In these dogs with biliary fistulas there was no evidence of inadequate digestion or absorption of protein, since the body weight remained uniform and the clinical condition was good, but the authors believe that in such dogs the inadequate production of hemoglobin may be related to disturbance of the hepatic function.

Gastrectomy was performed on young pigs by Petri and his co-workers.<sup>71</sup> After an initial period of good health the animals showed, in from one to two months, progressive hypochromic and microcytic anemia, arrest of growth, and changes in the skin, skeleton and central nervous system, together with hyperglobulinemia, cirrhosis of the liver and osteoporosis.

Dobriner and Rhoads<sup>140</sup> found an increase in the rate of excretion of coproporphyrin I in dogs after bleeding. The rate varied with the rate of formation of coproporphyrin III as new hemoglobin. The authors concluded that coproporphyrin I is probably a by-product in the synthesis of coproporphyrin III compounds and that the rate of excretion of coproporphyrin I is probably an index of hemopoietic activity under normal conditions.

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138 Fouts, P. J., Helmer, O. M., Lepkovsky, S., and Jukes, T. H. Production of Microcytic Hypochromic Anemia in Puppies on Synthetic Diet Deficient in Rat Antidermatitis Factor (Vitamin B<sub>6</sub>), *J. Nutrition* **16** 197, 1938.

139 Hawkins, W. B., Robschey-Robbins, F. S., and Whipple, G. H. Hemoglobin Production in Anemia as Influenced by the Bile Fistula, *J. Exper. Med.* **67** 89, 1938.

140 Dobriner, K., and Rhoads, C. P. Excretion of Coproporphyrin I Following Hemorrhage in Dogs, *J. Clin. Investigation* **17** 105, 1938.

*Nutritional Anemia of Children*—Congenital iron deficiency was studied in rats by Parsons and his associates,<sup>141</sup> and an analogy was drawn between their experimental observations and conditions which might be assumed to occur in infants. They found that in female rats receiving diets low in iron polycythemia and microcytosis developed but the hemoglobin values were unaltered, a picture regarded as the first stage in the evolution of anemia due to iron deficiency. The offspring of such rats showed microcytic anemia during lactation, but after weaning, if they were fed the special diet low in iron given to the mothers, the hemoglobin value became normal, polycythemia occurred and microcytosis persisted. Iron, supplemented by copper, had a curative effect on the changes in the blood. They concluded, by analogy, that anemia due to iron deficiency in human mothers may condition nutritional anemia in infants and, furthermore, that diets low in iron during pregnancy may, even in the absence of maternal anemia, lead to the same result. However, in comment, it may be stated that such an analogy is open to question, since the ratio of embryonic to maternal weight is at least three times as high in rats as in human beings and the duration of human gestation, during which the embryo may obtain iron and other materials from the maternal diet, is about twelve times as long as the period of gestation in the rat.

The earlier views of deposition of fetal storage iron in the liver as occurring at a disproportionately rapid rate during the later months of gestation have been challenged by Iob and Swanson,<sup>142</sup> who found a progressive increase in the total iron content of fetal liver but no change in the fetal iron per kilogram of desiccated defatted liver throughout the period of embryonic growth.

In a discussion of nutritional hypochromic anemia, Davidson and Fullerton<sup>143</sup> explained its presence in infancy on the basis of low birth weight. They pointed out that 80 per cent of the total iron contained within the infant's body is present in the circulating blood. The blood normally destroyed by hemolysis during the first two months of life supplies the iron stores subsequently used for the formation of new blood in response to growth needs. Consequently, the birth weight and the associated volume of blood have a much greater influence on the capacity to form new hemoglobin than is exerted by the iron stores in

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141 Parsons, L. G., Hickmans, E. M., and Finch, E. *Studies in Anaemia of Infancy and Childhood*. XI. The Effect of Iron Deficient Diets on the Size of the Red Blood Cells in Rats and in the Production of Microcytic Hypochromic Anaemia in Their Offspring, a Contribution to the Study of Congenital Iron Deficiency Anaemia in the Human Infant, *Arch. Dis. Childhood* **12** 369, 1937.

142 Iob, V., and Swanson, W. W. A Study of Fetal Iron, *J. Biol. Chem.* **124** 263, 1938.

143 Davidson, L. S. P., and Fullerton, H. W. Chronic Nutritional Hypochromic Anaemia, *Edinburgh M. J.* **45** 1, 1938.

the liver at the time of birth. Infections, according to these authors, have a deleterious effect on the formation of blood through three possible mechanisms: 1. Toxins may inhibit the formation of blood. 2. The excretion of iron may be increased. 3. The intake of iron may be reduced.

Schultz, Oldham and Morse<sup>144</sup> studied the iron metabolism of a normal child at three levels of iron intake, with and without supplementary crystalline vitamin B<sub>1</sub> (thiamin). They found the average retention of iron to be lower during periods of a high intake of vitamin B<sub>1</sub>, and they also concluded that for an optimum intake the child requires no more than 0.8 mg of iron per kilogram per day.

Hemoglobin estimations were obtained by Colver<sup>145</sup> for 310 children of preschool age from the poorer classes residing in the south London area. An incidence of 10 per cent of anemia up to the age of 3 years was found (hemoglobin, below 8.3 Gm per hundred cubic centimeters, 60 per cent [Haldane]), and good results were obtained from iron therapy. However, in untreated patients the incidence and severity of anemia decreased progressively from the first to the fourth year of life and the disease was rarely found after the fourth year. A study was carried out by Blackstock and Ritchie,<sup>146</sup> who found slightly lowered blood values for 31 children between the ages of 1 and 5 years whom they had reason to believe had been receiving poor diets. Iron and ammonium citrates led to improvement of the blood in the absence of dietary correction. Turk<sup>147</sup> and Skrivaneli and Leban-Klemenc<sup>148</sup> obtained good therapeutic results from the use of compounds of iron and cevitic acid in cases of anemia of prematurity, anemia associated with infection and nutritional anemias of children.

*Hypochromic Anemia of Adults*—Chronic nutritional hypochromic anemia is the term proposed by Davidson and Fullerton<sup>149</sup> for the common anemia of middle-aged women due to iron deficiency. The two important etiologic factors responsible for such anemia, according to these authors, are inadequate intake and increased demand for iron,

144 Schultz, F. W., Oldham, H., and Morse, M. Effect of Vitamin B<sub>1</sub> on the Iron Retention of a Normal Infant, *Am J Dis Child* **56** 735 (Oct) 1938.

145 Colver, T. Anemia in Preschool Children. Its Incidence in South London, *Lancet* **1** 245, 1938.

146 Blackstock, E., and Ritchie, J. M. Effect of Iron Administration in Cases of Subnutrition, *Brit M J* **1** 512, 1938.

147 Turk, E. Ce-Ferro bei Kinderanämien, *Med Klin* **34** 776, 1938.

148 Skrivaneli, N., and Leban-Klemenc, S. Die Eisentherapie sekundärer Anämien im Kindesalter, *Wien med Wchnschr* **88** 1161, 1938.

149 Davidson and Fullerton<sup>148</sup> Davidson, L. S. P., and Fullerton, H. W. Chronic Nutritional Hypochromic Anemia. II, *Edinburgh M J* **45** 102, 1938, III, *ibid* **45** 193, 1938.

and evidence is presented that direct dietary deficiency may play a principal part in its causation. They found an average daily intake of iron for women of the poorer classes of 7.3 mg. Of this they considered 75 per cent to be "available." They assumed that only half the available iron is absorbed, yielding an average daily absorption of only 2.5 mg. Davidson and Fullerton do not attribute to achlorhydria an important influence on iron absorption through its effect on the reaction of the contents of the small intestine but believe that in the absence of hydrochloric acid the liberation of dietary iron may be reduced. A vicious circle may be created in which long-continued dietary deficiency results in defective gastric secretion with achlorhydria as well as in anemia, the gastritis so produced then leads to digestive disorders, which further aggravate the effects of an inadequate diet. Diet therapy is valuable in the prevention but not in the treatment of chronic nutritional hypochromic anemia, and iron is most efficaciously administered in the form of its ferrous salts.

The tendency of the type of hypochromic anemia under discussion to occur in successive generations of the same family has been emphasized by Lundholm,<sup>150</sup> who has given case reports and inheritance charts. The disorder is characterized by specific changes in the blood and bone marrow but is not necessarily associated with achlorhydria, since, in the author's view, disturbance of gastric secretion usually follows the development of anemia. Thiele and Kuhl<sup>151</sup> believe that such anemia is a definite entity dependent, in part, on constitutional predisposition. Achlorhydria, according to their observations, is frequently present among the antecedents of patients with this form of anemia, but the etiologic role of achlorhydria cannot be proved. The disease is characterized by hypochromic and microcytic forms of anemia, atrophy of the mucous membranes of the upper part of the digestive tract, frequently leading to dysphagia, changes in the nails and paresthesias. Concomitant features which are of secondary diagnostic importance are the high degree of limitation to the female sex, the frequency of achlorhydria and the common finding of moderate enlargement of the spleen. The authors have advocated the use of iron in large doses as the most effective form of therapy for this disorder, and they consider iron ascorbate as of value and importance.

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150 Lundholm, I. Ueber den Erbgang bei Anaemia hypochromica essentialis (achylica et non achylica), *Acta med. Scandinav.*, 1938, supp. 89, p. 157.

151 Thiele, W., and Kuhl, H. Ueber die essentielle hypochrome Anämie. Pathogenese, *Klin. Wchnschr.* **17**: 1137, 1938, Symptomatologie mit besonderer Berücksichtigung des Plummer-Vinson-Syndroms, *ibid.* **17**: 1191, 1938, Therapie, *ibid.* **17**: 1219, 1938.

Waldenstrom<sup>152</sup> discussed the etiologic role of iron deficiency, or sideropenia, in disturbances of the epithelium even in the absence of anemia. He reported 3 cases of koilonychia without anemia in which iron therapy was of benefit, and he stated that certain lesions of the mucous membrane may respond favorably to such treatment. He suggested that plasma iron determinations may serve to disclose sideropenia in patients who have no anemia. Bode and Heyrodt<sup>153</sup> reported on 200 patients with chronic hypochromic anemia observed over a ten year period. They concluded that in cases of general weakness, especially in association with cardiac symptoms and neurasthenia in women, studies of the blood and gastric analysis should be done. According to them the administration of iron is the only therapeutic measure of value in this form of anemia. They employed 1 Gm of reduced iron daily and found that larger doses were unnecessary. In their experience the effect of iron was not enhanced by copper supplements. Schulten<sup>154</sup> emphasized that pernicious anemia and chronic hypochromic anemia may occur together, and he reported a case illustrating the coincidence of the two diseases. Study of the marrow, he stated, is a valuable procedure in the differential diagnosis. Meyers and his associates<sup>120</sup> reported a series of cases of chronic hypochromic anemia and discussed the multiple etiologic factors of the condition, including dietary deficiencies, achlorhydria, hypothyroidism, menorrhagia, other forms of blood loss and multiple pregnancies. Therapy, according to these authors, should include the administration of iron, attention to the diet, care of gastrointestinal and endocrine disorders and psychiatric treatment.

The influence of mucin on the absorption of iron has been investigated by Heath and his co-workers<sup>155</sup>. Mucin given together with relatively small amounts of iron in the form either of iron and ammonium citrates or of ferrous sulfate to patients with hypochromic anemia apparently inhibited the absorption of the metal from the intestine, as tested by study of the double-reticulocyte response. Using the same method of assay, Barker and Miller<sup>156</sup> secured evidence that the "Whipple liver fraction (secondary anemia fraction)" possesses some reticulo-

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152 Waldenstrom, J. Iron and Epithelium, Some Clinical Observations I. Regeneration of the Epithelium, *Acta med Scandinav*, 1938, supp 90, p 380

153 Bode, O. B., and Heyrodt, H. Die primäre hypochrome Anämie, *München med Wchnschr* **85** 1306, 1938

154 Schulten, H. Ueber die essentielle (primäre) hypochrome Anämie, *München med Wchnschr* **85** 1599, 1938 (Comment on article by Bode and Heyrodt<sup>153</sup>)

155 Heath, C. W., Minot, G. R., Pohle, F. J., and Alsted, G. The Influence of Mucin upon the Absorption of Iron in Hypochromic Anemia, *Am J M Sc* **195** 281, 1938

156 Barker, W. H., and Miller, D. K. Clinical Observations on the Whipple Liver Fraction (Secondary Anemia Fraction), *Am J M Sc* **195** 287, 1938

cytogenic properties apart from its content of iron. However, they found that the best clinical therapeutic results were obtained from the administration of large doses of inorganic iron. Friend<sup>157</sup> reported his observations on the use of iron ascorbate and concluded that the preparation gave good but not unusual results. He found, in terms of hemoglobin regeneration, that 10 mg of iron as the ascorbate (cevitamate) was equivalent to 32 mg of iron as iron and ammonium citrates when both were given by the intravenous route. When administered by mouth, 200 to 300 mg of iron as the ascorbate was equivalent to 500 to 700 mg of iron as iron and ammonium citrates, or 900 mg as reduced iron.

A number of general articles dealing with nutritional disorders in relation to anemia have appeared in the British literature during the past year.<sup>158</sup> For the most part the authors have discussed the factors affecting intake, absorption and utilization of iron, as well as other substances required for hemopoiesis.

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157 Friend, D. G. Iron Ascorbate in the Treatment of Anemia, *New England J. Med.* **219** 910, 1938.

158 Scott, R. B. The Iron-Deficiency Anaemias, *Lancet* **2** 549, 1938.  
Dauphine, J. A. Iron Requirement in Normal Nutrition, *Canad. M. A. J.* **39** 483, 1938. Ungley<sup>2</sup> Vaughan<sup>67</sup>

*(To Be Concluded)*

## News and Comment

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**Institute at University of Wisconsin**—The University of Wisconsin Medical School is to conduct an institute for the consideration of the blood and blood-forming organs, Sept 4 to 6, 1939. The program will include papers and round-table discussions by European and American workers in the field of hematology. In addition to the discussions, the following formal papers are to be presented:

Dr L J Witts, Oxford, England, Anemias Due to Iron Deficiency, Dr Cecil J Watson, Minneapolis, The Porphyrins and Diseases of the Blood, Dr Cornelius P Rhoads, New York, Aplastic Anemia, Dr E Meulengracht, Copenhagen, Denmark, Some Etiologic Factors in Pernicious Anemia and Related Macrocytic Anemias, Dr Harry Eagle, Baltimore, The Coagulation of Blood, Dr George R Minot, Boston, Anemias of Nutritional Deficiency, Dr Russell L Haden, Cleveland, The Nature of the Hemolytic Anemias, Dr Jacob Furth, New York, Experimental Leukemia, Dr Claude E Forkner, New York, Monocytic Leukemia and Aleukocythemic Leukemia, Dr Edward B Krumblhaar, Philadelphia, Hodgkin's Disease, Dr Louis K Diamond, Boston, The Erythroblastic Anemias, Dr Edwin E Osgood, Portland, Ore, Marrow Cultures, Dr Charles A Doan, Columbus, Ohio, The Reticuloendothelial System, Prof Hal Downey, Minneapolis, Infectious Mononucleosis, Dr Paul Reznikoff, New York, Polycythemia

Physicians and others who are interested are cordially invited. A detailed program may be obtained by addressing Dr Ovid O Meyer, Chairman of Program Committee, University of Wisconsin Medical School, Madison, Wis.

**Graduate Course in Internal Medicine**—Vanderbilt University Medical School announces a graduate course in internal medicine designed for those who desire special training in this field. The course will consist of supervised work with patients of the medical outpatient service, including the related specialties, experience in the diagnostic laboratories, assigned reading, seminars and conferences, including pathologic and radiologic conferences and autopsy study, and directed study and seminars in the preclinical sciences, particularly physiology and biochemistry. Special investigation of a particular problem in one of the divisions of internal medicine as the basis of a thesis will be required. The course will extend over a period of one year and will be open to any physician who has completed an internship, has had an additional year's experience as assistant resident in medicine or its equivalent and is acceptable to the school. The first course will begin on July 1, 1939, and is limited to 6 students. The tuition fee is \$300.

Three fellowships are available for this graduate course and provide tuition, board and lodging. They are open to those who meet the requirements mentioned and will be awarded on the basis of training and recommendations. Applications for the course and the fellowships should be sent to the Director of Postgraduate Instruction, Vanderbilt University Medical School, from whom further information regarding the course and the fellowships may be obtained.

**American Congress of Physical Therapy**—The eighteenth annual scientific and clinical session of the American Congress of Physical Therapy will be held on Sept 5 to 8, 1939, at the Hotel Pennsylvania in New York. Preceding these sessions, August 30 and 31 and September 1 and 2, the congress will conduct an intensive instruction seminar on physical therapy for physicians and technicians.

Registration is limited to 100 and is by application only. Further information concerning the seminar and preliminary program of the convention proper may be procured by addressing the American Congress of Physical Therapy, 30 North Michigan Avenue, Chicago.



## Book Reviews

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Studies on Proteinuria "Albuminuria" By J Bing Pp 151 Copenhagen : Levin & Munksgaard, Ejnar Munksgaard, 1936

The monograph is divided into four sections. In the first section the historical aspects of proteinuria are discussed, and special reference is made to the various mechanisms which produce it.

The second section describes the author's investigation of creatinine clearance as a measure of glomerular filtration. He believes that there is at present sufficient evidence that a close parallelism between the two exists but that there is not conclusive proof of it. An account is given of the special works throwing light on this subject.

The technic employed in the investigative work is explained in part 3. The author found that the total excretion of protein and albumin and thus of globulin, varies with the creatinine clearance. He points out that during protracted periods of proteinuria small quantities of proteins will make their way into the tubules, where they will be stored. In this way he explains the histogenesis of nephrosis, so that there is no question of "degeneration" in the tubules.

During the investigations patients were given 10 to 30 Gm of urea per os, but this seemed to have no influence on the parallelism between the excretion of protein and that of creatinine or on the constant glomerular protein content. When solution of posterior pituitary or histamine was given subcutaneously the creatinine clearance and the creatinine concentration index varied. However, the parallelism between the excretion of creatinine and that of protein still existed. Brief displacements occurred in some cases, and the concentration in the glomeruli increased, probably because of the increased permeability of the glomerular membrane. The same parallelism between the excretion of the protein and that of creatinine was found in a patient who had proteinuria of the Bence-Jones type. It is impossible at present to say whether or not proteinuria is dependent on the total protein content of the blood.

There is a parallelism also between the excretion of protein and that of urea, as both keep pace with the excretion of creatinine. It was found, however, that when solution of posterior pituitary or histamine is given the proteinuria is parallel to the urea clearance only when the latter corresponds to the creatinine clearance.

The cholesterolemia also was calculated, when conditions were constant, it was found to parallel the proteinuria and the creatinine and urea clearance only when the urea clearance corresponded to the creatinine clearance. When the conditions varied there were deviations between the proteinuria and the cholesterolemia, and the amount of cholesterol and protein excreted per minute in different patients was not constant. The variation in the cholesterol content of the blood (up to 37 per cent) had no influence on the quantity of cholesterol excreted.

The inverse ratio of the urine content to diuresis applies when the creatinine concentration index changes for the tubules, but not for the glomeruli.

The determination of the relative percentage of albumin in the total protein is preferable to that of the albumin-globulin quotient in studies of the relation of albumin and globulin in the blood and the urine.

The variations in the quantity of protein in the urine in twenty-four hour specimens are discussed in section 4. The author found that the degree of proteinuria rises and falls with the protein content of the diet and that there is a rise with ingestion of the acids and in the presence of fever. The percentage of albumin in the urine remains constant during the twenty-four hours and from day to day, when the conditions are not varied, and, unlike the total protein excretion, it is not affected by the protein content of the diet, nor are the total protein content of the blood and its percentage of albumin affected.

The total excretion of protein is found to be greater in patients with nephrosis and amyloidosis than in those with glomerulonephritis and nephrosclerosis but apparently there is no significant difference in the calculated glomerular contents in the various forms of Bright's disease. In the individual patient the degree of proteinuria varies with changes in infiltration value and glomerular permeability. The author finds almost inverse proportionality between these two values.

There seems to be no definite difference, either, in the percentages of albumin in the urine in the different types of Bright's disease. It is decreased in the late chronic stages because of a corresponding fall in the percentage of albumin in the blood or because of altered glomerular permeability. The renal factor measures this permeability, which is found in the majority of cases to be between 1 and 3. In cases of nephrosis and amyloidosis it is relatively high, and the low percentage of albumin in these cases is caused by similar conditions in the blood. In patients with chronic glomerulonephritis and contracting nephrosis it is found to be lower.

These studies are illustrated by case reports, and many tables and charts aid greatly in the interpretation of the text. This interesting monograph on an important phase of renal disorders should be of interest to every internist, as well as to investigators of renal disease.

**Cardiovascular Disease in General Practice** By Terence East, F R C P, London, Physician-in-Charge of Cardiological Department, King's College Hospital. Price, 10s 6d. Pp. x + 206, with 43 illustrations. London: H. K. Lewis & Co., Ltd., 1938.

There seems to be a worldwide movement afoot to educate the physician in general practice. A few years ago small books on various practical topics designed to appeal to the general practitioner were published in both France and Germany, and now a series on general practice is forthcoming from Great Britain.

In the latter part of 1934 and during the early months of 1935 there appeared in the *British Medical Journal* a group of articles dealing mainly with treatment and written by well known teachers. Later these articles were assembled in book form and published under the title, "Treatment in General Practice." There were two volumes. They were put out by H. K. Lewis and Company. They were well printed, of convenient size to fit into one's pocket and extremely readable. They were popular, too. The first edition appeared in March 1936, it was reprinted in March 1937, and a second edition came out in June 1938.

The series on general practice appears to be an offshoot of "Treatment in General Practice," elaborating in monographic form certain important topics. It, too, is published by H. K. Lewis and Company. In external appearance the volume on cardiovascular disease is almost an identical twin of the first volume of "Treatment in General Practice." The main difference is that the latter is printed on slightly smoother paper by the University Press of Glasgow and sells for 8 shillings and 6 pence, whereas Dr. East's book is printed in London by the Whitehouse Press on somewhat coarser paper and in larger type and is a trifle more expensive. By strange coincidence, the chapter on the management of auricular fibrillation and flutter in "Treatment in General Practice" was written by the same Dr. East, who now appears to have expanded this chapter into a book.

The book is readable. It repeats from a slightly different angle and from one pen what already has been told by several authors in the book on treatment. An interesting minor difference is that electrocardiography is scarcely mentioned in East's book, although in "Treatment in General Practice" the subject receives due emphasis. The author, one imagines, does not believe that many general practitioners are familiar with tracings and their interpretations, and this may be a valid assumption, despite the relative inexpensiveness of the portable machine and the frequency with which, on this side of the Atlantic at least, it is used.

The book is worth meeting. It makes a pleasant companion for a railroad journey, if the other volumes of this series are as attractive, they will embellish any medical library.

**The Chemistry of the Sterids** By Harry Sobotka Price, \$8 50 Pp 634  
Baltimore Williams & Wilkins Company, 1938

This book consists of a correlation and systematization of the literature on the chemical and physical properties of the sterids. It is intended as a companion to the volume entitled "The Chemistry of the Bile Acids and Related Substances," which was previously published by the author, the two volumes being independent but, at the same time, overlapping in many respects.

The present volume consists of eleven chapters, which include a brief historical survey of sterid chemistry and of methods of structural research and an exhaustive discussion of the chemical and physical characteristics of the sterids. The author has included much on the hormones of sterid constitution. There is a lengthy classified catalog of the sterids and their derivatives, containing their structural formulas, systematic designations, melting points, data on optical activity and other physical constants, as well as information on their occurrence, formation and synthesis, to which are added accounts of their chemical reactions and transformations from all sources available on Jan 1, 1937. In addition, there is an extensive bibliography of domestic and foreign literature on the sterids. The index is quite complete.

Sobotka has accumulated all the data on sterid chemistry, which existed in a chaotic state in the literature, and has admirably organized it in a simple and accurate fashion for the investigator attempting to master the extensive literature on the subject. The book should serve as an indispensable supplement to the handbooks on organic chemistry and should conserve much time for those interested in problems of sterid chemistry.

**The Pneumonias** By Hobart A. Reimann, M D, Professor of Medicine, Jefferson Medical College, Philadelphia, Formerly Professor of Medicine, University of Minnesota, Formerly Associate Professor of Medicine, Peiping Union Medical College, Peiping, China. With a foreword by Rufus Cole. Cloth Price, \$5 50 Pp 381, with 111 illustrations. Philadelphia W B Saunders Company, 1938.

Dr. Reimann has made a substantial contribution by clearly and forcibly expressing the modern points of view on the pneumonias. He constantly emphasizes the etiologic classification of the acute pulmonary infections and their specific treatments. He correctly insists that every effort must be taken to ascertain the causative organism in each case at the earliest moment. Thus pneumonia becomes an acute medical emergency requiring the facilities of a modern hospital, a good laboratory and often a clinical specialist. In a discussion of treatment, the nature of the subject requires a rather dogmatic presentation, but most views expressed here are orthodox. Some readers will wish for a more detailed discussion of oxygen therapy. With regard to the use of sulfanilamide in pneumococcic pneumonia, the author reserves judgment. He effectively disposes of many outmoded types of treatment. There is a valuable and well illustrated chapter on roentgenography. In this book the atypical, rare and mixed types of pneumonia are completely discussed for the first time.

Books like this, which have been developed from the author's experience, have a practical value not attained by more traditional presentations.

**The Patient and the Weather** Volume IV, part 3 **Organic Disease, Surgical Problems** By William F. Petersen, M D, assisted by Margaret E. Milliken, M S. Cloth Price, \$10 Pp 651, with 482 illustrations. Ann Arbor, Mich. Edwards Brothers, Inc., 1938.

The material for this massive work, dealing with the effect of the weather on the human system, has been carefully compiled and painstakingly arranged. However, one must be a meteorologist to appreciate its value fully.

This book is of interest to the general practitioner as it covers such subjects as infection, inflammation, ulcers, disease of the gallbladder, pancreatitis and ectopic pregnancy. Here and there the author has added numerous graphs, which he has taken great pains to prepare.

The author considers all illnesses and pathologic conditions as due to changes in temperature, polar fronts and other meteorologic factors. This, of course, is not medically scientific, as no reference is made to the bacteriologic or to the pathologic aspects of the various conditions described.

The reviewer of this monograph cannot recommend it as a textbook. However, it is worthy of reading and rereading so that some idea can be obtained of the influence of the weather on the human system.

**The Chemistry of the Amino Acids and Proteins** Edited by Carl L. A. Schmidt, M.S., Ph.D., Professor of Biochemistry, University of California. Price, \$7.50. Pp. 1,031, with 260 illustrations and 152 tables. Springfield, Ill. Charles C. Thomas, Publisher, 1938.

Sixteen collaborators in the United States and Netherlands have joined to make this the most detailed and inclusive volume in the English language dealing with the proteins. It stands as a worthy successor to the obsolete monograph of Brailsford Robertson and to Jacques Loeb's brilliant but sharply delimited work. Dealing as it does with every phase of protein chemistry, it will be welcomed as a working tool by biochemists, immunologists and many organic chemists. Practitioners of medicine, unless unusually conversant with the language of physical chemistry, will find the body of the book too difficult to read, the last two chapters dealing with applications to immunity and nutrition, can be read with interest and profit by any physician.

**Clinical Roentgenology of the Digestive Tract** By Maurice Feldman, M.D., Assistant Professor of Gastroenterology, University of Maryland, Associate Roentgenologist, Sinai Hospital, Assistant in Gastroenterology, Mercy Hospital, Baltimore. Price, \$10. Pp. 1,014, with 358 illustrations and 179 tables. Baltimore. William Wood & Company, 1938.

This text presents a thorough consideration of gastrointestinal disease. It is written primarily for the roentgenologist and gastroenterologist. The author has systematically presented each subject as far as possible with regard to incidence, etiology, age and sex, site, association with other conditions, pathology, clinical diagnosis and roentgen diagnosis.

In addition to the alimentary tract, disease of the gallbladder, and cholecystography, and also pancreatic disease are especially well presented.

The literature is extensively reviewed, with inclusion of numerous references. As a whole the book is clear and thorough, it is adequately illustrated and it will be an invaluable reference work.

In compiling material for a text on as extensive a subject as this, the author is to be commended on his complete and understanding presentation.

**Verhandlungen der deutschen Gesellschaft für Kreislaufforschung, Eleventh Meeting** Edited by Prof. Dr. E. Koch. Price, 11.25 marks. Pp. 430 with 131 colored illustrations, together with charts. Dresden. Theodor Steinkopff, 1938.

This issue of the proceedings of the Deutsche Gesellschaft für Kreislaufforschung consists of forty-three reports, lectures and discussions by as many different observers on the subject of circulatory collapse. The discussions include such subjects as circulatory collapse as related to internal medicine and surgery, significance of muscle tonus in postoperative shock, carbonic acid and collapse, changes in capillary permeability in the capillary beds and many other physiologic, pharmacologic and therapeutic aspects of the subject. The discussions are exten-

sive and cover the subject completely. There are many illustrations accompanying the presentations, which increase the value considerably.

This issue of the proceedings is recommended to all interested in normal and abnormal peripheral vascular physiology and also to clinicians, who so frequently encounter circulatory collapse.

**Intoxications et carences alimentaires** Edited by Maurice Loeper Price, 60 francs Pp 259 Paris Masson et Cie, 1938

This book, edited by Maurice Loeper, who was assisted by fifteen contributors, consists of sixteen chapters dealing with alimentary intoxications and deficiencies. Digestive hypersensitivity, secretory insufficiencies and alimentary residues, the defense and protection of the gastrointestinal tract, micro-organisms of the gastrointestinal tract and their urinary elimination, vascular and nervous difficulties of digestive origin, cutaneous reactions of digestive origin, the effects of the avitaminoses on the gastrointestinal tract, local and general therapy of digestive insufficiency and other subjects are considered. The authors present the problems from a clinical point of view, attempting to aid the clinician with an explanation of mechanistic, diagnostic and therapeutic problems associated with intoxications and physiologic dysfunctions of alimentary origin. The significance of primary alimentary dysfunction from the patient's standpoint and its clinical understanding are presented in a simple and clear fashion.

The book is recommended to internists and especially gastroenterologists, who frequently encounter such alimentary problems in their clinical endeavors.

**A Biological Approach to the Problem of Abnormal Behavior** By Milton Harrington Price, \$4 Pp 459, with 12 illustrations Lancaster, Pa The Science Press Printing Co., 1938

The importance of the psychologic element in disease is being more and more emphasized and rightly so. Every physician soon learns that the majority of his patients have no gross anatomic lesion, they suffer because of an abnormal reaction to a situation which either is entirely environmental or perhaps has some slight physical basis. A good many books have appeared recently dealing with the problems of disease from this standpoint, of which this is one. The reviewer does not feel qualified to criticize the soundness of this particular writer's point of view, but the book is interesting, and thinking along these lines is undoubtedly profitable for every physician who seeks to go beyond the old approach of explaining his patients' troubles in terms of morbid anatomy.

**Pseudo-Tuberculosis in Man Part I Besnier-Boeck's Disease** By Prof. I. Snapper and Dr. A. W. Pompen **Part II Regional Ileitis** By Prof. I. Snapper Price, Hfl 7.50 Pp 90, with 13 illustrations Haarlem, Netherlands de Erven F. Bohn, 1938

This handsome volume with its beautiful illustrations, contains lectures given by Professor Snapper at the University of London on the sarcoids of Boeck and on regional ileitis. In addition to general descriptions there are interesting detailed case reports. The discussion emphasizes especially the differentiation of these conditions from true tuberculosis.

**Klinische Infektionslehre Einführung in die Pathogenese der Infektionskrankheiten** By Dr. Felix O. Horing, Oberarzt der II medizinischen Klinik und Dozent an der Universität München Price, 10.50 marks Pp 184 Berlin Julius Springer, 1938

This book is a clinical presentation of the subject of infectious diseases, largely in a textbook manner, and would be suitable for use by medical students. It does not seem to contain anything that would be of special interest to specialists in bacteriology or clinical pathology.

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